Drug Data Report 2010, 32(9): 843-933

CCC: 1579-1793/2010

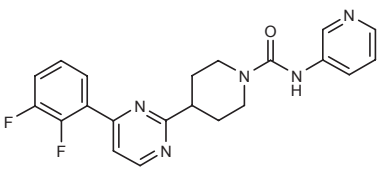
MONOGRAPHS

ANALGESIC AND ANESTHETIC DRUGS

TREATMENT OF PAIN

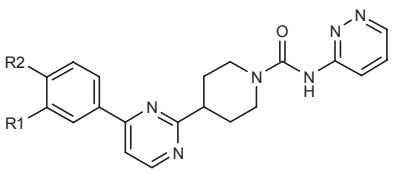
700592

4-[4-(2,3-Difluorophenyl)pyrimidin-2-yl]-*N*-(3-pyridyl)piperidine-1-carboxamide



C21H19F2N5O; Mol wt: 395.4053

ACTION – Fatty-acid amide hydrolase inhibitor that displayed analgesic activity in mice in an acetic acid-iduced writhing test (49.4% inhibition of writhing at 10 mg/kg p.o.). Reported to be useful for the treatment of pain, depression and anxiety. Related compounds include:



Compound	R1	R2	Formula
700593	H	H	$C_{20}H_{20}N_6O$
700595	F	H	$C_{20}H_{19}FN_6O$
700596	H	F	$C_{20}H_{19}FN_6O$

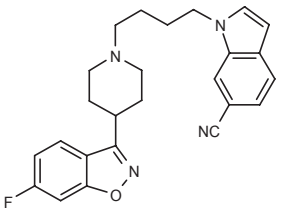
SOURCE – Takeda.

REFERENCES

1. Kori, M. and Kouno, M. (Takeda Pharmaceutical Co., Ltd.) *Piperidine derivative.* WO 2010064597.

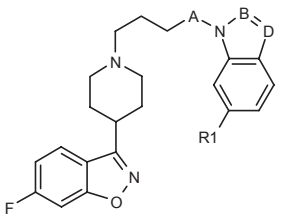
701105

1-[4-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]butyl]-1*H*-indole-6-carbonitrile



C25H25FN4O; Mol wt: 416.4906

ACTION – 5-HT2A receptor antagonist (K_i = 1.9670 nM; IC_{50} = 2.9223 nM) and 5-HT reuptake inhibitor that inhibited the binding of [^{3}H]-ketanserin to 5-HT2A receptors by 99.3% and inhibited 5-HT reuptake by 105% at 10 µmol/L. Expected to be useful for the treatment of pain. Related compounds include:



Compound	R1	A	B	D	Formula
701100	Cl	O	N	N	$C_{21}H_{21}ClFN_5O_2$
701101	F	CH2	CH	N	$C_{23}H_{24}F_2N_4O$
701103	CN	CH2	N	CH	$C_{24}H_{24}FN_5O$

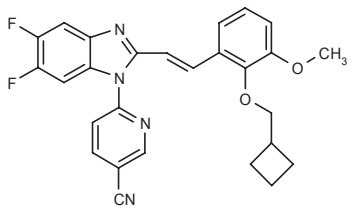
SOURCE – Nhwa Pharma.

REFERENCES

1. Li, J. et al. (Nhwa Pharma Corp.) *Benzisoxazole piperidinyl derivatives, pharmaceutical compositions comprising the derivatives and their use.* CN 101759693, WO 2010072147.

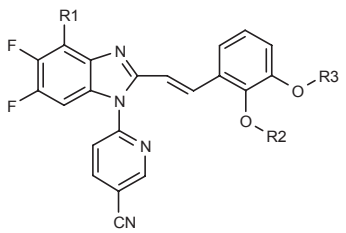
701254

6-[2-[2(*E*)-[2-(Cyclobutylmethoxy)-3-methoxyphenyl]vinyl]-5,6-difluoro-1*H*-benzimidazol-1-yl]pyridine-3-carbonitrile



C27H22F2N4O2; Mol wt: 472.4860

ACTION – Transient receptor potential cation channel TRPV3 inhibitor that suppressed human TRPV3 activation in CHO cells (IC_{50} < 50 nM in a calcium uptake assay). Reported to be useful for the treatment of chronic, acute and postoperative pain, and inflammation, including osteoarthritis and rheumatoid arthritis. Related compounds include:



Compound	R1	R2	R3	Formula
701258	F	C5H11	Me	$C_{27}H_{23}F_3N_4O_2$
701261	H	cyclobutyl-CH2	CHF2	$C_{27}H_{20}F_4N_4O_2$
701263	H	cyclopentyl	CHF2	$C_{27}H_{20}F_4N_4O_2$

SOURCE – Glenmark Pharmaceuticals.

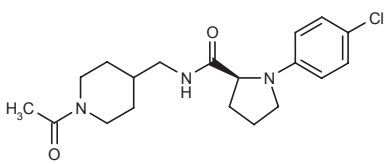
REFERENCES

1. Lingam, V.S.P. et al. (Glenmark Pharmaceuticals SA) *Fused imidazole derivatives as TRPV3 antagonist*. WO 2010073128.

701915

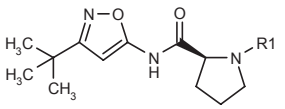
N-(1-Acetylpiperidin-4-ylmethyl)-1-(4-chlorophenyl)-L-prolinamide

N-(1-Acetylpiperidin-4-ylmethyl)-1-(4-chlorophenyl)pyrrolidine-2(*S*)-carboxamide

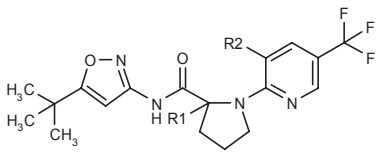


C19H26ClN3O2; Mol wt: 363.8820

ACTION – Cannabinoid CB2 receptor agonist with an EC_{50} of 0.015 nM for human CB2 receptors expressed in CHO cells in a cAMP asssay. Described as useful for the treatment of pain, as well as inflammatory and immunological diseases, coronary heart disease, renal, hepatic, gastrointestinal and neurodegenerative diseases, among others. Related compounds include:



Compound	R1	Formula
701902	2-cyclohexenyl-CH2	$C_{19}H_{29}N_3O_2$
701905	5-Cl-3-F-2-Pyr	$C_{17}H_{20}ClFN_4O_2$
701908	5-CF3-2-Pyr	$C_{18}H_{21}F_3N_4O_2$
701909	3-Cl-5-CF3-2-Pyr	$C_{18}H_{20}ClF_3N_4O_2$



Compound	R1	R2	Isomer	Formula
701910	Me	H	S	$C_{19}H_{23}F_3N_4O_2$
701912	H	Cl		$C_{18}H_{20}ClF_3N_4O_2$
701913	H	H	S	$C_{18}H_{21}F_3N_4O_2$

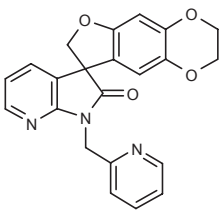
SOURCE – Boehringer Ingelheim.

REFERENCES

1. Berry, A. et al. (Boehringer Ingelheim Pharma GmbH & Co. KG) *Pyrrolidine compounds which modulate the CB2 receptor*. WO 2010077836.

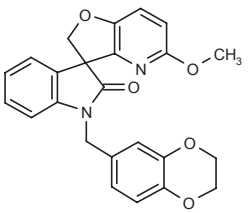
702093

1'-(Pyridin-2-ylmethyl)-1',2',2,3-tetrahydrospiro[furo[2,3-*g*][1,4]-benzodioxin-8,3'-pyrrolo[2,3-*b*]pyridin]-2'-one



C22H17N3O4; Mol wt: 387.3881

ACTION – Voltage-gated sodium channel blocker that gave an IC_{50} of 1-100 nM in guanidine influx assays. Reported to be useful for the treatment of pain, hypercholesterolemia, benign prostatic hyperplasia, pruritus and cancer. Another exemplified compound is:



702094: C24H20N2O5

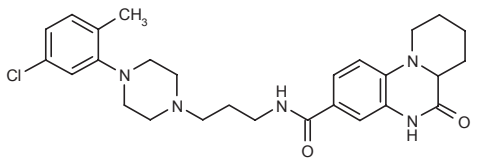
SOURCE – Xenon Pharmaceuticals.

REFERENCES

1. Cadieux, J.-J. et al. (Xenon Pharmaceuticals Inc.) *Spiro-oxindole-derivatives as sodium channel blockers*. WO 2010078307.

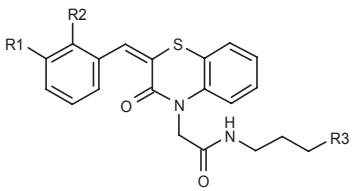
702103

N-[3-[4-(5-Chloro-2-methylphenyl)piperazin-1-yl]propyl]-6-oxo-6,6a,7,8,9,10-hexahydro-5*H*-pyrido[1,2-*a*]quinoxaline-3-carboxamide

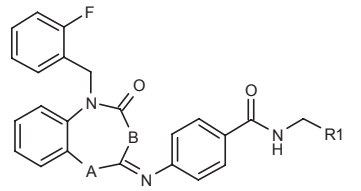


C27H34ClN5O2; Mol wt: 496.0440

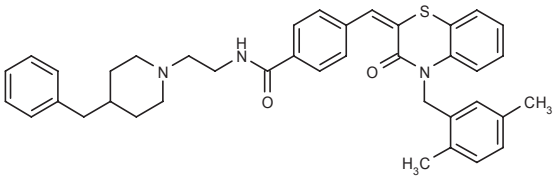
ACTION – Inhibitor of the high affinity nerve growth factor receptor (IC_{50} = 0.085 μM), reported to be useful for the treatment of pain, cancer, restenosis, atherosclerosis, psoriasis, thrombosis and demyelinating diseases, as well as anxiety, epilepsy, burns, smoking, inflammation and immune-related disorders, amomg others. Related compounds include:



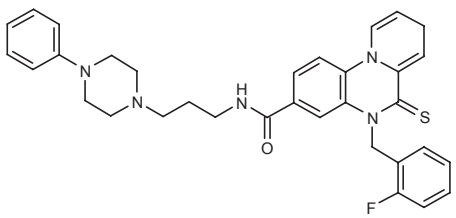
Compound	R1	R2	R3	Isomer	Formula
702107	Cl	H	N(Me)CH2Ph	Z	$C_{28}H_{28}ClN_3O_2S$
702108	H	Cl	4-(4-F-Ph)-1-Piz	E	$C_{30}H_{30}ClFN_4O_2S$



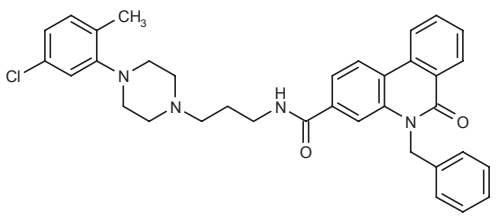
Compound	R1	A	B	Formula
702109	H	O	bond	$C_{23}H_{18}FN_3O_3$
702113	1-pyrrolidinyl-CH2CH2	S	CH2	$C_{30}H_{31}FN_4O_2S$



702106: C39H41N3O2S



702111: C33H34FN5OS



702112: C35H35ClN4O2

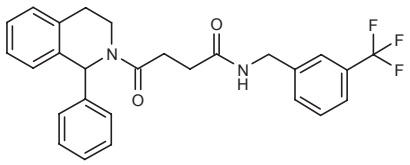
SOURCE – VM Discovery.

REFERENCES

1. Wu, J.J.-Q. and Wang, L. (VM Discovery, Inc.) *Compositions of protein receptor tyrosine kinase inhibitors*. WO 2010077680.

702489

4-Oxo-4-(1-phenyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-*N*-[3-(trifluoromethyl)benzyl]butyramide



C27H25F3N2O2; Mol wt: 466.4948

ACTION – Voltage-gated potassium channel K(v)7.2/7.3 modulator that activated human channels expressed in CHO-K1 cells (EC_{50} = 1.90 μM) in fluorescence assays and displayed agonist activity in patch clamp assays (efficacy = 78% at 10 μM). Compound at 4.64 mg/kg i.v. reduced formalin-induced nociceptive pain in rats by 40%. Reported to be useful for the treatment of pain. Further applications include epilepsy, urinary incontinence, cognitive disorders, bipolar disorders, mania, anxiety, migraine, substance dependency and dystonia-associated dyskinesia.

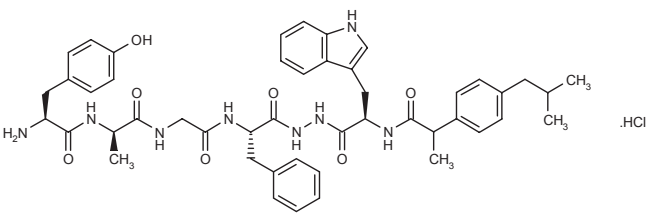
SOURCE – Grünenthal.

REFERENCES

1. Kühnert, S. et al. (Grünenthal GmbH) *Substituted 4-(1,2,3,4-tetrahydroisoquinolin-2-yl)-4-oxobutyric acid amide as KCNQ2/3 modulators*. US 2010152234, WO 2010075973.

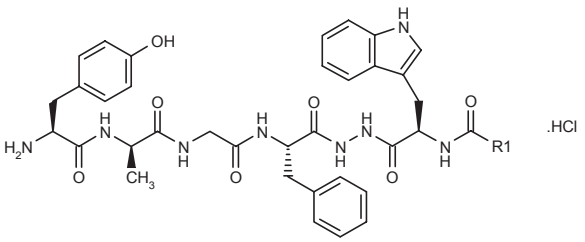
704154

N-[*N*-[2-(4-Isobutylphenyl)propionyl]-D-tryptophanyl]-*N*'-(L-tyrosyl-D-alanyl-glycyl-L-phenylalanyl)hydrazide hydrochloride



C47H57ClN8O7; Mol wt: 881.4580

ACTION – Opioid receptor ligand with analgesic activity in animal models of pain. Reported to be useful for the treatment of pain caused particularly by inflammation. Related compounds include:



Compound	R1	Formula
704157	OCH2Ph	$C_{42}H_{47}ClN_8O_8$
704159	2-OH-Ph	$C_{41}H_{45}ClN_8O_8$

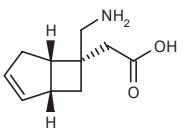
SOURCE – Action for Development of Research.

REFERENCES

1. Lipkowski, A. (Action for Development of Research Sp zoo) *A method of producing a novel opioid peptide*. WO 2010077154.

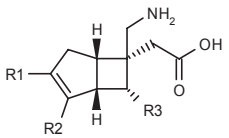
704161

2-[(1*R*,5*S*,6*R*)-6-(Aminomethyl)bicyclo[3.2.0]hept-2-en-6-yl]acetic acid

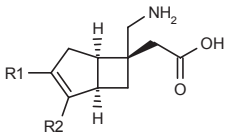


C10H15NO2; Mol wt: 181.2316

ACTION – Voltage-gated calcium channel α2-δ subunit ligand that inhibited the binding of [^{3}H]-gabapentin with an IC_{50} of 40 nM. Compound displayed an ID_{50} of 10.4 mg/kg in mechanical models of pain hypersensitivity in mice. Reported to be useful for the treatment of pain, as well as central nervous system-related disorders. Related compounds include:



Compound	R1	R2	R3	Formula
704164	H	H	H	$C_{10}H_{15}NO_2$
704166	H	H	(R*)-Me	$C_{11}H_{17}NO_2$
704167	Et	H	H	$C_{12}H_{19}NO_2$
704168	H	Et	H	$C_{12}H_{19}NO_2$



Compound	R1	R2	Formula
704165	H	H	$C_{10}H_{15}NO_2$
704170	H	Et	$C_{12}H_{19}NO_2$
704171	H	Pr	$C_{13}H_{21}NO_2$
704172	Pr	H	$C_{13}H_{21}NO_2$

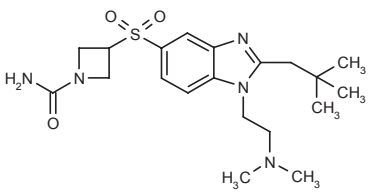
SOURCE – Daiichi Sankyo.

REFERENCES

1. Shimada, K. et al. (Daiichi Sankyo Co., Ltd.) *Olefin compound*. WO 2010079668.

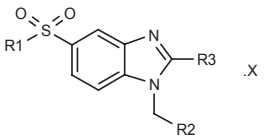
704666

3-[1-[2-(Dimethylamino)ethyl]-2-(2,2-dimethylpropyl)-1*H*-benzimidazol-5-ylsulfonyl]azetidine-1-carboxamide



C20H31N5O3S; Mol wt: 421.5570

ACTION – Cannabinoid CB2 receptor agonist (EC_{50} < 0.03 μM for human CB2 receptors expressed in CHO-K1 cells) with 800-fold selectivity versus the CB1 receptor. Claimed for use in the treatment of pain, neurological disorders, inflammation, respiratory disorders, gastrointestinal disorders, autoimmune diseases, renal disorders, diabetes and cardiovascular disorders, among others. Related compounds include:



Compound	R1	R2	R3	X	Formula
704667	1-(MeSO2)-3-azetidinyl-CH2	cyclopropyl	t-BuCH2		$C_{21}H_{31}N_3O_4S_2$
704671	1-(MeSO2)-4-Pip-CH2	cyclopropyl	t-Bu		$C_{22}H_{33}N_3O_4S_2$
704672	1-(2-oxo-4-imidazolidinyl--CO)-4-Pip-CH2	cyclopropyl	t-BuCH2		$C_{26}H_{37}N_5O_4S$
704674	1-(NH2CO)-3-azetidinyl	1-Ac-4-Pip	t-BuCH2		$C_{24}H_{35}N_5O_4S$
704675	1-(NH2CO)-3(S)-pyrrolidinyl	cyclopropyl	t-BuCH2		$C_{21}H_{30}N_4O_3S$
704676	1-Et-3-azetidinyl	CH2N(Me)2	t-BuCH2		$C_{21}H_{34}N_4O_2S$
704677	1-Me-3(R)-pyrrolidinyl	CH2N(Me)2	t-BuCH2	2HCl	$C_{21}H_{36}Cl_2N_4O_2S$

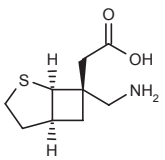
SOURCE – RaQualia.

REFERENCES

1. Ando, K. and Iwata, Y. (RaQualia Pharma Inc.) *N-Substituted saturated heterocyclic sulfone compounds with CB2 receptor agonistic activity*. WO 2010084767.

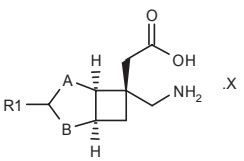
704698

2-[(1*R**,5*S**,7*R**)-7-(Aminomethyl)-2-thiabicyclo[3.2.0]hept-7-yl]-acetic acid



C9H15NO2S; Mol wt: 201.2860

ACTION – Voltage-gated calcium channel α2-δ subunit ligand that inhibited the binding of [^{3}H]-gabapentin to the human channel expressed in HEK-293 cells with an IC_{50} of 44 nM. Claimed fur use in the treatment of pain, amyotrophic lateral sclerosis, epilepsy, generalized anxiety and restless legs syndrome. Other representative compounds are:



Compound	R1	A	B	X	Formula
704699	H	CH2	S	HCl	$C_9H_{16}ClNO_2S$
704700	Et	S	CH2		$C_{11}H_{19}NO_2S$

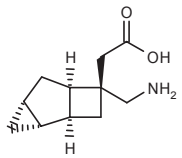
SOURCE – Daiichi Sankyo.

REFERENCES

1. Shimada, K. et al. (Daiichi Sankyo Co., Ltd.) *Hetero atom-containing compound*. WO 2010084797.

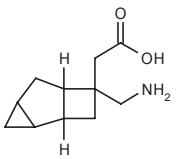
704728

2-[(1*R**,2*S**,4*S**,6*S**,7*R**)-7-(Aminomethyl)tricyclo[4.2.0.0^{2,4}]oct-7-yl]acetic acid

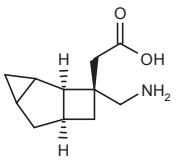


C11H17NO2; Mol wt: 195.2582

ACTION – Voltage-gated calcium channel $\alpha 2$-δ subunit ligand that inhibited the binding of [^{3}H]-gabapentin to the human channel expressed in HEK-293 cells with an IC_{50} of 17 nM. Claimed for use in the treatment of pain, amyotrophic lateral sclerosis, epilepsy, generalized anxiety disorder and restless legs syndrome. Other representative compounds are:



Compound	Isomer	Formula
704731	1R*,2R*,4R*,6S*,7R*	$C_{11}H_{17}NO_2$
704737	1R*,2S*,4S*,6S*,7R*	$C_{11}H_{17}NO_2$



704729: C11H17NO2

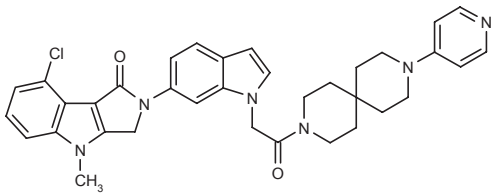
SOURCE – Daiichi Sankyo.

REFERENCES

1. Shimada, K. and Onishi, Y. (Daiichi Sankyo Co., Ltd.) *Tricyclic compound*. WO 2010084798.

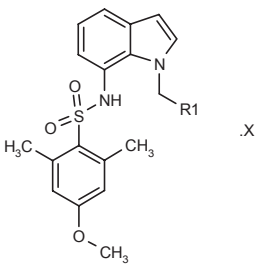
705794

8-Chloro-4-methyl-2-[1-[2-oxo-2-[9-(4-pyridyl)-3,9-diazaspiro-[5.5]undec-3-yl]ethyl]-1*H*-indol-6-yl]-1,2,3,4-tetrahydropyrrolo-[3,4-*b*]indol-1-one



C35H35ClN6O2; Mol wt: 607.1440

ACTION – Bradykinin B1 receptor antagonist that inhibited rat and human receptors expressed in CHO-K1 cells by 106 and 100%, respectively, at 10 μM. Reported to be useful for the treatment of acute, chronic and neuropathic pain, as well as migraine, diabetes, respiratory disorders, inflammatory bowel disease, neurological disorders, rheumatoid arthritis, septic shock, reperfusion syndrome and obesity. Related compounds include:



Compound	R1	X	Formula
705838	9-(4-Pyr)-3,9-diazaspiro[5,5]undec-3-yl-CO		$C_{33}H_{39}N_5O_4S$
705840	3-[6-(1-Pip-CH2)-1,2,3,4-tetrahydroisoquinolin-2-yl]-1-pyrrolidinyl-CO	2HCl	$C_{38}H_{49}Cl_2N_5O_4S$
705841	9-(1-azetidinyl)-3-azaspiro[5,5]undec-3-yl-CO		$C_{32}H_{42}N_4O_4S$
705842	9-(4-Pyr-O)-3-azaspiro[5,5]undec-3-yl-CO		$C_{34}H_{40}N_4O_5S$
705843	1-(4-Pyr)-4-Pip-CH2CH2NHCOCH2		$C_{32}H_{39}N_5O_4S$
705845	4-(4-Pyr)-1-Piz-(CH2)3N(Me)CO		$C_{32}H_{40}N_6O_4S$

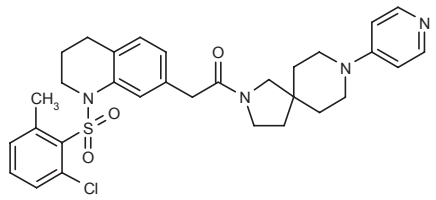
SOURCE – Grünenthal.

REFERENCES

1. Schunk, S. et al. (Grünenthal GmbH) *Substituted indole compounds as bradykinin receptor 1 modulators*. US 2010222324, WO 2010089084.

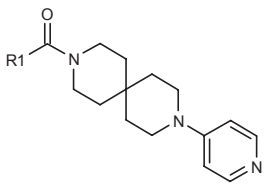
705892

2-[1-(2-Chloro-6-methylphenylsulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl]-1-[8-(4-pyridyl)-2,8-diazaspiro[4.5]dec-2-yl]ethanone

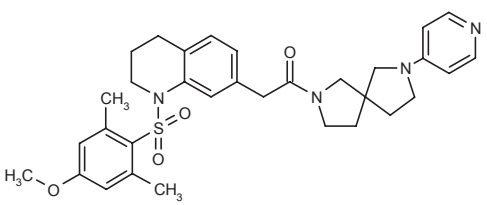


C31H35ClN4O3S; Mol wt: 579.1530

ACTION – Bradykinin B1 receptor antagonist that inhibited rat and human receptors expressed in CHO-K1 cells by 102 and 100%, respectively, at 10 µM. Reported to be useful for the treatment of chronic pain and neuropathic pain. Further applications include migraine, diabetes, respiratory disorders, rheumatoid arthritis, septic shock and reperfusion syndrome. Related compounds include:



Compound	R1	Formula
705884	4-[2,6-(Me)2-4-MeO-PhSO2]-3,4-dihydro-2H-1,4-benzoxazin-6-yl-CH2	$C_{33}H_{40}N_4O_5S$
705885	1-[2,6-(Me)2-4-MeO-PhSO2]-2,3-dihydro-1H-indol-6-yl-CH2	$C_{33}H_{40}N_4O_4S$
705888	7-[2,6-(Me)2-4-MeO-PhCH2]-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-2-yl	$C_{31}H_{40}N_6O_2$
705890	2-(5-Cl-2-thienyl-CO)-1,2,3,4-tetrahydro-7-isoquinolyl	$C_{29}H_{31}ClN_4O_2S$
705893	2-[2,6-(Me)2-4-MeO-PhSO2]-2,3-dihydro-1H-isoindol-5-yl	$C_{32}H_{38}N_4O_4S$
705895	7-[2,6-(Me)2-4-MeO-PhSO2]-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazin-1-yl	$C_{30}H_{38}N_6O_4S$



705882: C32H38N4O4S

SOURCE – Grünenthal.

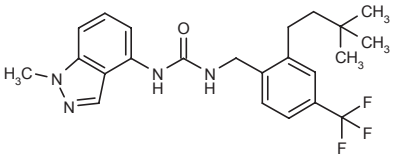
REFERENCES

1. Schunk, S. et al. (Grünenthal GmbH) *Substituted spiro-amides as B1R modulators*. US 2010234340, WO 2010089127.

ABT-116*[1-5]

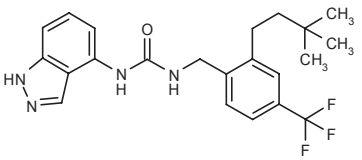
472691

N-[2-(3,3-Dimethylbutyl)-4-(trifluoromethyl)benzyl]-*N*'-(1-methyl-1*H*-indazol-4-yl)urea



C23H27F3N4O; Mol wt: 432.4819

ACTION – Transient receptor potential channel TRPV1 antagonist (IC_{50} = 15 and 7 nM, respectively, in a Ca^{2+} uptake assay in HEK-293 cells) with selectivity for human versus rat channels (IC_{50} = 277 nM). Compound inhibited carrageenan-induced inflammatory hyperalgesia (ED_{50} = 25 µmol/kg p.o.) and iodoacetate-induced arthritic pain (ED_{50} = 66 µmol/kg p.o.) in rats. Oral bioavailability was 58% in rats. Potentially useful for the treatment of neuropathic and inflammatory pain, urinary incontinence and bladder overactivity. Another representative compound is:



698921[2,3]**:** C22H25F3N4O

SOURCE – Abbott.

REFERENCES

1. Lee, C.-H. et al. (Abbott Laboratories Inc.) *Indazole derivatives that inhibit TRPV1 and uses thereof*. EP 2054390, JP 2010501592, WO 2008024945.

2. Lukin, K.A. et al. (Abbott Laboratories Inc.) *Methods for making central nervous system agents that are TRPV1 antagonists*. US 2010016611, WO 2009117626.

3. Brown, B.S. et al. *Discovery of TRPV1 antagonist ABT-116*. Bioorg Med Chem Lett 2010, 20(11): 3291.

4. Yu, S. et al. *Synthesis of a TRPV1 receptor antagonist*. J Org Chem 2009, 74(24): 9539.

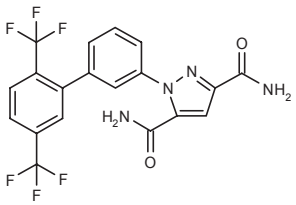
5. Yu, S. et al. *Synthesis of ABT-116, a TRPV1 receptor antagonist*. 238th ACS Natl Meet (Aug 16-20, Washington) 2009, Abst ORGN 770.

*Identified compound **472691** (see **472688**) Drug Data Rep 2008, 030(03): 0196.

BPD-1

706393

1-[2',5'-Bis(trifluoromethyl)biphenyl-3-yl]-1*H*-pyrazole-3,5-dicarboxamide



C19H12F6N4O2; Mol wt: 442.3146

ACTION – Voltage-gated sodium channel Na(v)1.7 blocker that gave IC_{50} values of 0.810 and 1.32 µM, respectively, against Na(v)1.7 and Na(v)1.5 channels, with selectivity over Na(v)1.8 channels (IC_{50} = 2000 µM). Compound dose-dependently (3-30 mg/kg p.o.) inhibited neuropathic pain in a spinal nerve ligation model in rats and exhibited no significant effect on motor coordination in the rotarod test at 30 and 100 mg/kg p.o. Oral bioavailability was 60 and 33%, respectively, in rats and dogs. Potentially useful for the treatment of pain, inflammation and other central nervous system related disorders.

SOURCE – Merck & Co.

REFERENCES

1. Chakravarty, P.K. et al. (Merck & Co., Inc.) *Biaryl substituted pyrazoles as sodium channel blockers*. CA 2520804, EP 1615895, JP 2006522130, US 2006183785, US 7589116, WO 2004092140.

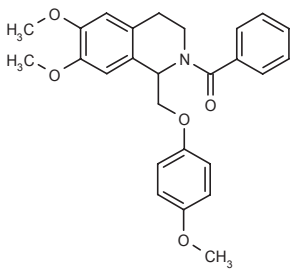
2. Tyagarajan, S. et al. *Substituted biaryl pyrazoles as sodium channel blockers for the treatment of neuropathic pain*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 292.

DIQ-1180

705239

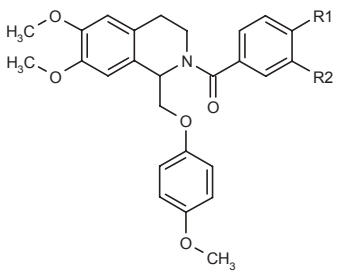
1-[6,7-Dimethoxy-1-(4-methoxyphenoxymethyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]-1-phenylmethanone

Compound-1180

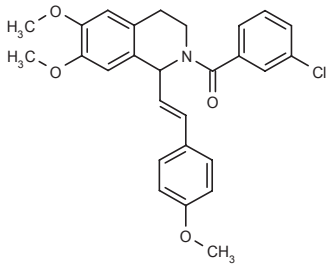


C26H27NO5; Mol wt: 433.4963

ACTION – Selective NMDA receptor subtype 2C agonist with an EC_{50} < 13 µM. Potentially useful for the treatment of pain, bone disorders such as osteoporosis, schizophrenia, Parkinson's disease, cognitive disorders, anxiety, bipolar disorders, depression, stroke, traumatic brain injury, epilepsy and related neurological events. Related compounds include:



Compound	R1	R2	Formula
Compound-1390 [705241]	H	Cl	$C_{26}H_{26}ClNO_5$
Compound-1426 [705242]	H	CF3	$C_{27}H_{26}F_3NO_5$
Compound-1425 [705243]	H	Me	$C_{27}H_{29}NO_5$
Compound-1368 [705244]	Cl	H	$C_{26}H_{26}ClNO_5$
Compound-1180-18 [705245]	F	Cl	$C_{26}H_{25}ClFNO_5$



Compound-1180-31 [705246]: C27H26ClNO4

SOURCE – Emory University, Atlanta, GA (US).

REFERENCES

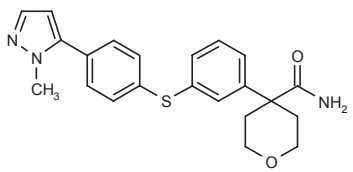
1. Traynelis, S.F. et al. (Emory University) *Subunit selective NMDA receptor potentiators for the treatment of neurological conditions*. WO 2010088414.

PF-4191834

473340

4-[3-[4-(1-Methyl-1*H*-pyrazol-5-yl)phenylsulfanyl]phenyl]tetrahydropyran-4-carboxamide

PF-04191834



C22H23N3O2S; Mol wt: 393.5020

ACTION – 5-Lipoxygenase inhibitor (IC_{50} = 229 and 328 nM, respectively, in fluorescent and orthogonal spectrophotometric assays; IC_{50} = 130 nM in a human whole blood cell assay). Compound 5 mg/kg b.i.d. showed complete inhibition of leukotriene B_4 production and at 1-10 mg/kg p.o. it reversed mechanical hyperalgesia in rats. Phase II clinical trials for the treatment of osteoarthritis are under way.

SOURCE – Pfizer.

REFERENCES

1. Graneto, M.J. et al. (Pfizer Inc.;Pfizer Products Inc.) *Pyrazole analogs*. EP 2097407, JP 2010511601, US 2008125474, US 7772269, WO 2008065493.

2. Masferrer, J.L. et al. *Pharmacology of PF-4191834, a novel, selective non-redox 5-lipoxygenase inhibitor effective in inflammation and pain*. J Pharmacol Exp Ther 2010, 334(1): 294.

3. *A study of the safety and efficacy Of PF-04191834 in patients with osteoarthritis of the knee (NCT01147458)*. ClinicalTrials.gov Web Site 2010, July 13.

4. *PF-04191834 single dose bronchodilatory study in asthma (NCT00723021)*. ClinicalTrials.gov Web Site 2008, Sept 23.

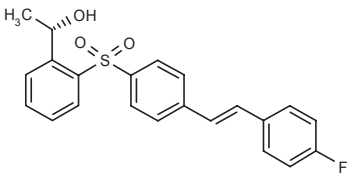
5. *To test the relative bioavailability Of PF-04191834 when dosed as an immediate release tablet compared with solution following single and multiple dosing (NCT01064804)*. ClinicalTrials.gov Web Site 2010, July 13.

PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

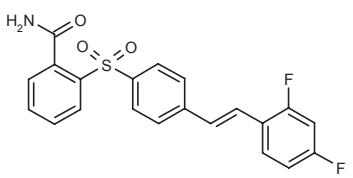
421846*[1-3]

1(*S*)-[2-[4-[2(*E*)-(4-Fluorophenyl)vinyl]phenylsulfonyl]phenyl]-ethanol



C22H19FO3S; Mol wt: 382.4480

ACTION – Selective 5-HT2A receptor antagonist (K_i = 1.32 and 65 nM, respectively, for human 5-HT2A and 5-HT2C receptors), with 40% receptor occupancy at 10 mg/kg p.o. in rats. Potentially useful for the treatment of insomnia, schizophrenia and anxiety. Another representative compound is:



700688[1,3]: C21H15F2NO3S

SOURCE – Merck Sharp & Dohme.

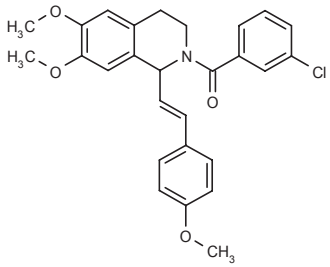
REFERENCES

1. Castro Pineiro, J.L. et al. (Merck Sharp & Dohme Ltd.) *Diarylsulfones as 5-HT2A antagonists*. JP 2008510785, WO 2006021805.

2. Gilligan, M. et al. (Merck Sharp & Dohme Ltd.) *Arylsulphonylstilbene derivatives for treatment of insomnia and related conditions*. WO 2006021806.

3. Ladduwahetty, T. et al. *Non-basic ligands for aminergic GPCRs: The discovery and development diaryl sulfones as selective, orally bioavailable 5-HT2A receptor antagonists for the treatment of sleep disorders*. Bioorg Med Chem Lett 2010, 20(12): 3708.

*Identified compound **421846** Drug Data Rep 2006, 028(05): 0418.



Compound-1180-31 [705246]: C27H26ClNO4

SOURCE – Emory University, Atlanta, GA (US).

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PF-4191834

473340

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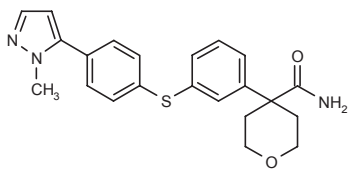
PF-04191834



C22H23N3O2S; Mol wt: 393.5020

ACTION – 5-Lipoxygenase inhibitor (IC_{50} = 229 and 328 nM, respectively, in fluorescent and orthogonal spectrophotometric assays; IC_{50} = 130 nM in a human whole blood cell assay). Compound 5 mg/kg b.i.d. showed complete inhibition of leukotriene B_4 production and at 1-10 mg/kg p.o. it reversed mechanical hyperalgesia in rats. Phase II clinical trials for the treatment of osteoarthritis are under way.

SOURCE – Pfizer.

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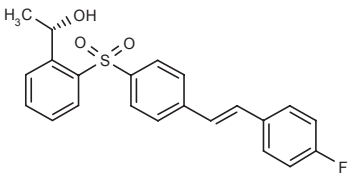
PSYCHOPHARMACOLOGIC DRUGS

TREATMENT OF SLEEP DISORDERS

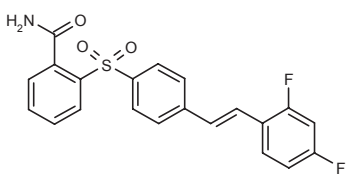
421846*[1-3]

1(*S*)-[2-[4-[2(*E*)-(4-Fluorophenyl)vinyl]phenylsulfonyl]phenyl]-ethanol



C22H19FO3S; Mol wt: 382.4480

ACTION – Selective 5-HT2A receptor antagonist (K_i = 1.32 and 65 nM, respectively, for human 5-HT2A and 5-HT2C receptors), with 40% receptor occupancy at 10 mg/kg p.o. in rats. Potentially useful for the treatment of insomnia, schizophrenia and anxiety. Another representative compound is:



700688[1,3]: C21H15F2NO3S

SOURCE – Merck Sharp & Dohme.

REFERENCES

1. Castro Pineiro, J.L. et al. (Merck Sharp & Dohme Ltd.) *Diarylsulfones as 5-HT2A antagonists*. JP 2008510785, WO 2006021805.

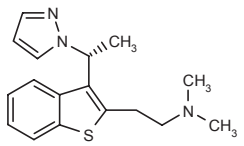
2. Gilligan, M. et al. (Merck Sharp & Dohme Ltd.) *Arylsulphonylstilbene derivatives for treatment of insomnia and related conditions*. WO 2006021806.

3. Ladduwahetty, T. et al. *Non-basic ligands for aminergic GPCRs: The discovery and development diaryl sulfones as selective, orally bioavailable 5-HT2A receptor antagonists for the treatment of sleep disorders*. Bioorg Med Chem Lett 2010, 20(12): 3708.

*Identified compound **421846** Drug Data Rep 2006, 028(05): 0418.

695100

(–)-*N*,*N*-Dimethyl-2-[3-[1(*R*)-(1*H*-pyrazol-1-yl)ethyl]-1-benzothien-2-yl]ethylamine



C17H21N3S; Mol wt: 299.4340

ACTION – Histamine H1 receptor antagonist (K_i = 4.4 nM) that showed a K_i of > 10,000 nM for the muscarinic acetylcholine M1 receptor and 200-fold selectivity over H3 and > 1,000-fold selectivity over M3 and 5-HT2A receptors. Reported to be useful for the treatment of insomnia, inducing sleep, sedation or hypnosis.

SOURCE – Neurocrine Biosciences.

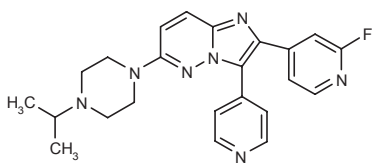
REFERENCES

1. Beaton, G. et al. (Neurocrine Biosciences, Inc.) *Sleep-inducing compounds and methods related thereto*. US 2006014797, US 7393865, WO 2006019497.

2. Moree, W.J. et al. *Novel benzothiophene H1-antihistamines for the treatment of insomnia*. Bioorg Med Chem Lett 2010, 20(7): 2316.

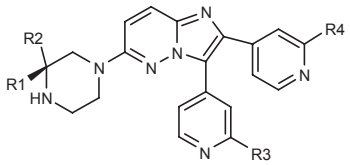
700167

2-(2-Fluoropyridin-4-yl)-6-(4-isopropylpiperazin-1-yl)-3-(4-pyridyl)-imidazo[1,2-*b*]pyridazine



C23H24FN7; Mol wt: 417.4820

ACTION – Casein kinase CKI-δ and/or -ε inhibitor that reduced the phosphorylation of casein catalyzed by CKI-δ (IC_{50} = 287 nM) in a [^{33}P]-ATP filter plate assay. Compound prolonged circadian periods by 1 h in luciferase reporter gene assays using Mper1-luc Rat-1 (P2C4) fibroblasts with a CE δ(t + 1h) of 6-273 nM. Reported to be useful for the treatment of circadian rhythm disorders, as well as anxiety, depression, bipolar disorders, substance abuse dependence, Alzheimer's disease, cancer and inflammation. Related compounds include:



Compound	R1	R2	R3	R4	Formula
700168	Me	Me	H	H	$C_{22}H_{23}N_7$
700169	Me	Me	Me	H	$C_{23}H_{25}N_7$
700170	H	H	H	H	$C_{20}H_{19}N_7$
700171	Me	H	H	F	$C_{21}H_{20}FN_7$

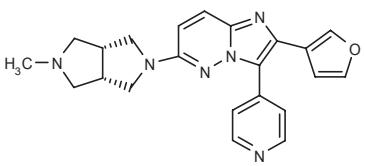
SOURCE – sanofi-aventis.

REFERENCES

1. Barrague, M. et al. (sanofi-aventis) *Derivatives of 6-cycloamino-2,3-di-pyridinyl-imidazo[1,2-b]-pyridazine, preparation and therapeutic application thereof*. FR 2940284, WO 2010070238.

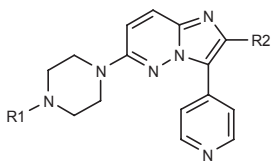
700621

cis-2-(3-Furyl)-6-(5-methylperhydropyrrolo[3,4-*c*]pyrrol-2-yl)-3-(4-pyridyl)imidazo[1,2-*b*]pyridazine



C22H22N6O; Mol wt: 386.4497

ACTION – Casein kinase CKI-ε and/or -δ inhibitor that suppressed CKI-ε with an IC_{50} of 15 nM in a [^{33}P]-ATP filter plate assay and prolonged circadian periods by 1 h in luciferase reporter gene assays using Mper1-luc Rat-1 (P2C4) fibroblasts with a CE δ (t + 1h) of 17 nM. Reported to be useful for the treatment of circadian rhythm disorders, depression, anxiety and substance abuse dependence, inflammation, mood disorders and cancer. Related compounds include:



Compound	R1	R2	Formula
700623	H	5-Me-2-thienyl	$C_{20}H_{20}N_6S$
700625	CH2CH2OH	5-Cl-2-thienyl	$C_{21}H_{21}ClN_6OS$
700626	Me	3-thienyl	$C_{20}H_{20}N_6S$

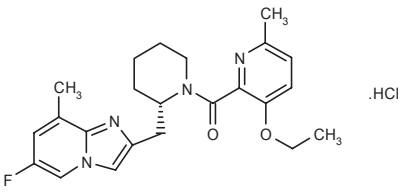
SOURCE – sanofi-aventis.

REFERENCES

1. Chiang, Y. et al. (sanofi-aventis) *Derivatives of 6-cycloamino-2-thienyl-3-(pyridin-4-yl)imidazo[1,2-b]-pyridazine and 6-cycloamino-2-furanyl-3-(pyridin-4-yl)imidazo[1,2-b]-pyridazine, preparation and therapeutic application thereof*. FR 2940285, WO 2010070237.

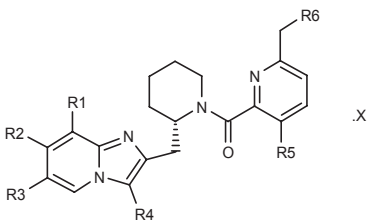
701343

1-(3-Ethoxy-6-methylpyridin-2-yl)-1-[2(*S*)-(6-fluoro-8-methylimidazo[1,2-*a*]pyridin-2-ylmethyl)piperidin-1-yl]methanone hydrochloride



C23H28ClFN4O2; Mol wt: 446.9450

ACTION – Orexin receptor antagonist reported to be useful for the treatment of sleep disorders. Further applications include mood disorders, particularly depression and anxiety, substance abuse and dependence, and eating disorders. Other representative compounds are:



Compound	R1	R2	R3	R4	R5	R6	X	Formula
701346	Me	H	H	H	cyclopropyl-CH2O	H		$C_{25}H_{30}N_4O_2$
701347	Me	Me	H	H	i-BuO	H		$C_{26}H_{34}N_4O_2$
701349	F	H	H	H	PrO	H	HCl	$C_{23}H_{28}ClFN_4O_2$
701351	Me	H	H	Cl	cyclopropyl-CH2O	H	HCl	$C_{25}H_{30}Cl_2N_4O_2$
701353	Me	Me	H	H	EtO	Me	HCl	$C_{25}H_{33}ClN_4O_2$
701354	Me	Me	H	H	5-Me-2-oxazolyl	H		$C_{26}H_{29}N_5O_2$
701356	Me	H	F	H	2-pyrimidinyl	H		$C_{25}H_{25}FN_6O$

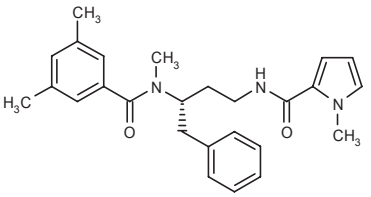
SOURCE – GlaxoSmithKline.

REFERENCES

1. Alvaro, G. and Amantini, D. (GlaxoSmithKline plc) *Piperidine derivatives useful as orexin antagonists*. WO 2010072722.

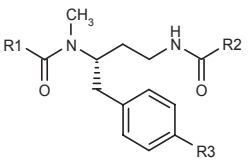
705154

N-[3(*S*)-[*N*-(3,5-Dimethylbenzoyl)-*N*-methylamino]-4-phenylbutyl]-1-methyl-1*H*-pyrrole-2-carboxamide



C26H31N3O2; Mol wt: 417.5432

ACTION – Orexin receptor antagonist that inhibited human OX2 receptors expressed in CHO cells with a K_d of 0.007 and 0.002 μM, respectively, in radioligand binding and FLIPR assays, and showed selectivity over human OX1 receptors (K_d = 0.176 and 0.230 μM, respectively). Reported to be useful for the treatment of sleep disorders, eating disorders, substance abuse and dependence and Alzheimer's disease. Related compounds include:



Compound	R1	R2	R3	Formula
705162	4-indolyl	1-Me-2-benzimidazolyl	H	$C_{29}H_{29}N_5O_2$
705166	3,5-(CF3)2-Ph	2-Pyr	H	$C_{26}H_{23}F_6N_3O_2$
705171	1-Naph	1-Me-2-benzimidazolyl	F	$C_{31}H_{29}FN_4O_2$
705177	1-Naph	2-Pyr	F	$C_{28}H_{26}FN_3O_2$
705182	1-Naph	2-Pyr	Cl	$C_{28}H_{26}ClN_3O_2$
705184	3-F-5-MeO-Ph	1-Me-2-pyrrolyl	H	$C_{25}H_{28}FN_3O_3$
705186	3-Me-Ph	1-Me-2-pyrrolyl	H	$C_{25}H_{29}N_3O_2$
705188	3,4-(MeO)2-Ph	1-Me-2-pyrrolyl	H	$C_{26}H_{31}N_3O_4$
705190	3-EtO-Ph	1-Me-2-pyrrolyl	H	$C_{26}H_{31}N_3O_3$
705193	3-CF3O-Ph	1-Me-2-pyrrolyl	H	$C_{25}H_{26}F_3N_3O_3$

SOURCE – Novartis.

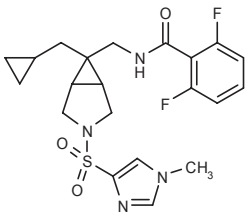
REFERENCES

1. Behnke, D. et al. (Novartis AG) *4-Aryl-butane-1,3-diamides*. WO 2010086366.

ANTIPSYCHOTIC DRUGS

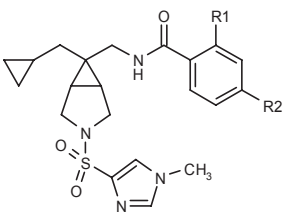
702098

N-[6-(Cyclopropylmethyl)-3-(1-methyl-1*H*-imidazol-4-ylsulfonyl)-3-azabicyclo[3.1.0]hex-6-ylmethyl]-2,6-difluorobenzamide



C21H24F2N4O3S; Mol wt: 450.5020

ACTION – Glycine transporter GlyT-1 inhibitor (IC_{50} = 4 nM for inhibition of [^{14}C]-glycine uptake into human placental choriocarcinoma JAR cells), reported to be useful for the treatment of neurological and psychiatric disorders such as schizophrenia, as well as depression, bipolar disorders, cognitive disorders, amnestic, attention and eating disorders, delirium, anxiety and obesity, among others. Related compounds include:



Compound	R1	R2	Formula
702096	CF3	H	$C_{22}H_{25}F_3N_4O_3S$
702097	Cl	Cl	$C_{21}H_{24}Cl_2N_4O_3S$

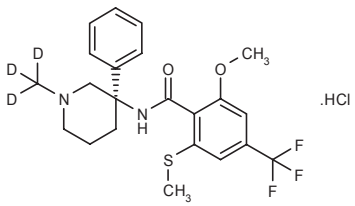
SOURCE – Vanderbilt University, Nashville, TN (US).

REFERENCES

1. Lindsley, C.W. et al. (The Vanderbilt University) *3.1.0 Bicyclic GlyT1 inhibitors and methods of making and using same*. WO 2010078348.

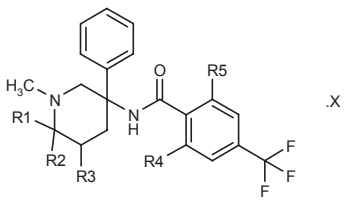
705174

2-Methoxy-6-(methylsulfanyl)-*N*-[(3*R**)-1-(trideuteromethyl)-3-phenylpiperidin-3-yl]-4-(trifluoromethyl)benzamide hydrochloride



C22H26ClF3N2O2S; Mol wt: 477.9860

ACTION – Glycine transporter GlyT-1 inhibitor that suppressed glycine uptake in mGlyT-1b-transfected CHO cells (IC_{50} = 0.01 μM). Reported to be useful for the treatment of psychosis including schizophrenia, dementia including Alzheimer's disease, pain, memory and learning dysfunction, and attention deficit disorders. Other representative compounds are:



Compound	R1	R2	R3	R4	R5	Isomer	X	Formula
705181	H	H	H	H	cyclopropyl	racemic		$C_{23}H_{25}F_3N_2O$
705183	H	H	H	SMe	OMe	3R	HCl	$C_{22}H_{26}ClF_3N_2O_2S$
705185	Me	Me	H	SMe	OMe	racemic	HCl	$C_{24}H_{30}ClF_3N_2O_2S$
705187	H	Me	H	SMe	OMe	3R*, 6R*		$C_{23}H_{27}F_3N_2O_2S$
705189	H	Me	H	SMe	OMe	3R*, 6S*		$C_{23}H_{27}F_3N_2O_2S$
705191	H	H	Me	SMe	OMe	3R*, 5S*		$C_{23}H_{27}F_3N_2O_2S$
705192	H	H	Me	H	Et	3R*, 5S*		$C_{23}H_{27}F_3N_2O$

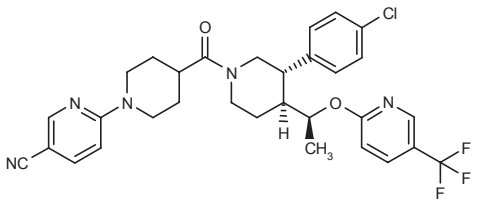
SOURCE – Roche.

REFERENCES

1. Kolczewski, S. et al. (F. Hoffmann-La Roche AG) *Aroylamino-and heteroaroylamino-substituted piperidines as GlyT-1 inhibitors*. US 2010197715, WO 2010086251.

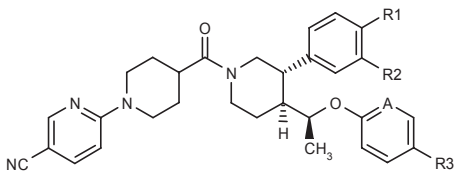
705216

6-[4-[3(*S*)-(4-Chlorophenyl)-4(*S*)-[1(*S*)-[5-(trifluoromethyl)pyridin-2-yloxy]ethyl]piperidin-1-ylcarbonyl]piperidin-1-yl]pyridine-3-carbonitrile



C31H31ClF3N5O2; Mol wt: 598.0580

ACTION – Tachykinin NK3 receptor antagonist that inhibited the binding of [^{3}H]-SR-142801 to human NK3 receptors expressed in HEK-293 cells (K_i = 0.0002 μM). Reported to be useful for the treatment of psychosis including schizophrenia, anxiety, depression, pain, Parkinson's disease and attention deficit hyperactivity disorder. Other representative compounds are:



Compound	R1	R2	R3	A	Formula
705217	Cl	H	Cl	N	$C_{30}H_{31}Cl_2N_5O_2$
705218	Cl	H	CN	N	$C_{31}H_{31}ClN_6O_2$
705219	Cl	H	F	N	$C_{30}H_{31}ClFN_5O_2$
705220	Cl	H	F	CH	$C_{31}H_{32}ClFN_4O_2$
705221	Cl	H	Cl	CH	$C_{31}H_{32}Cl_2N_4O_2$
705223	F	F	Cl	N	$C_{30}H_{30}ClF_2N_5O_2$
705224	F	F	CN	N	$C_{31}H_{30}F_2N_6O_2$

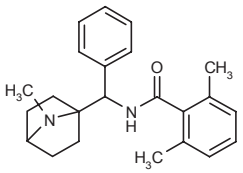
SOURCE – Roche.

REFERENCES

1. Knust, H. et al. (F. Hoffmann-La Roche AG) *Piperidine derivatives as NK3 receptor antagonists*. US 2010197697, WO 2010086259.

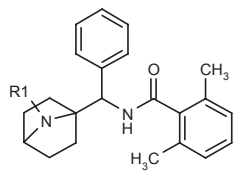
705544

2,6-Dimethyl-*N*-[1-(7-methyl-7-azabicyclo[2.2.1]hept-1-yl)-1-phenylmethyl]benzamide



C23H28N2O; Mol wt: 348.4812

ACTION – Glycine transporter GlyT-1 inhibitor that displayed an IC_{50} of 0.000772 μM for inhibition of glycine uptake in CHO cells transfected with mGlyT-1b. Potentially useful for the treatment of psychosis, cognitive disorders, bipolar disorders, depression, anxiety and pain. Related compounds include:



Compound	R1	Formula
705538	cyclopropyl-CH2	$C_{26}H_{32}N_2O$
705539	CH2CH2OH	$C_{24}H_{30}N_2O_2$
705543	i-Pr	$C_{25}H_{32}N_2O$

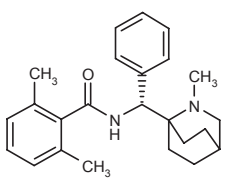
SOURCE – AstraZeneca.

REFERENCES

1. Albert, J.S. et al. (AstraZeneca AB) *2-Aza-bicyclo[2.2.1]heptane compounds and uses thereof*. WO 2010087762.

706472

2,6-Dimethyl-*N*-[1(*R*)-(2-methyl-2-azabicyclo[2.2.2]oct-1-yl)-1-phenylmethyl]benzamide



C24H30N2O; Mol wt: 362.5078

ACTION – Isoquinucline-based glycine transporter GlyT-1 uptake inhibitor (IC_{50} = 1 nM) that reversed MK-801-induced locomotor activity and increased retention in mouse novel object recognition tests (MED = 3 and 1 µmol/kg, respectively). Potentially useful for the treatment of mood disorders, cognitive disorders, psychosis and anxiety.

SOURCE – AstraZeneca.

REFERENCES

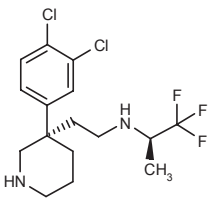
1. Albert, J.S. et al. (AstraZeneca plc;AstraZeneca AB) *2-Azabicyclo(2.2.2)octane derivatives as modulators of the glycine transporter I receptor*. US 2009030033, WO 2009013535.

2. Albert, J.S. et al. *Isoquinucline-based GlyT1 inhibitors for schizophrenia: Discovery, optimization, synthesis, and in vivo pharmacology*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 287.

TREATMENT OF MOOD DISORDERS

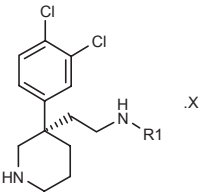
700315

N-[2-[3(*S*)-(3,4-Dichlorophenyl)piperidin-3-yl]ethyl]-1,1,1-trifluoropropan-2(*R*)-amine



C16H21Cl2F3N2; Mol wt: 369.2530

ACTION – Inhibitor of dopamine (DAT) and norepinephrine transporters (K_i = 4.4 and 1.2 nM, respectively, in HEK-293F cells). Reported to be useful for the treatment of atypical and melancholic depression, cocaine abuse, attention deficit hyperactivity disorder and disruptive behavior disorders. Related compounds include:



Compound	R1	X	Isomer	Formula
700318	(S)-CH(CF3)Me	2HCl		$C_{16}H_{23}Cl_4F_3N_2$
700319	C(Me)2CONHMe			$C_{18}H_{27}Cl_2N_3O$
700320	CH(CF3)CH2OH		A	$C_{16}H_{21}Cl_2F_3N_2O$
700321	CH(CF3)CH2OH		B	$C_{16}H_{21}Cl_2F_3N_2O$
700322	C(Me)2CF3			$C_{17}H_{23}Cl_2F_3N_2$
700324	CH2CH(OH)CF3			$C_{16}H_{21}Cl_2F_3N_2O$

SOURCE – AstraZeneca.

REFERENCES

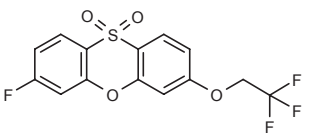
1. Bernstein, P. et al. (AstraZeneca AB) *Quaternary piperidine derivatives and uses thereof*. WO 2010071575.

CX-157

439503

3-Fluoro-7-(2,2,2-trifluoroethoxy)phenoxathiin 10,10-dioxide

TriRima™
Tyrima™



C14H8F4O4S; Mol wt: 348.2700

ACTION – Selective and reversible monoamine oxidase inhibitor (IC_{50} = 19.3 ng/L in human brain) that was well tolerated in patients with major depressive disorders at a dose of 180 mg p.o. twice daily. In phase I studies compound showed no serious adverse events in healthy volunteers. Oral bioavailability was 34% (suspension-fed monkeys) and 47% (emulsion-fed monkeys). Phase II studies with 60 mg/day twice daily have been completed in subjects with major depressive disorder. Potentially useful for the treatment of depression and neurodegenerative diseases.

SOURCES – CeNeRx BioPharma; Krenitsky.

REFERENCES

1. Brand, B.S. and Free, J.C. (CeNeRx BioPharma, Inc.) *Oral sustained release antidepressant formulation*. WO 2010080977.

2. Brand, B.S. et al. (CeNeRx BioPharma, Inc.) *Oral enteric antidepressant formulation*. WO 2010080970.

3. Brot, E.C.A. et al. (CeNeRx BioPharma, Inc.) *Polymorphic form of fluoro-7-(2,2,2-trifluoroethoxy)phenoxathiin-10,10-dioxide*. US 2008009542, WO 2008008273.

4. Harfenist, M. et al. (Krenitsky Prmaceuticals, Inc.) *Pharmacologically active compounds and use*. JP 2002501475, WO 1998012190.

5. Asgharnejad, M. et al. *Results of a double-blind, placebo-controlled study of CX157 (TriRima), a reversible specific monoamine oxidase a inhibitor, in the treatment of major depressive disorder*. 27th World Congr CINP (June 6-10, Hong Kong) 2010, Abst 2.

6. Burch, D. et al. *Steady state pharmacokinetics and safety of CX157 (TriRima), a reversible specific monoamine oxidase an inhibitor*. 27th World Congr CINP (June 6-10, Hong Kong) 2010, Abst 5.

7. Fielding, R.M. et al. *Pharmacokinetics and oral bioavailability of CX157, a reversible selective MAO-A inhibitor, in primates*. AAPS J 2007, 9(Suppl. 2): Abst W4433.

8. Fowler, J. et al. *Evidence for robust and reversible brain MAO-A inhibition by CX-157 in healthy normal volunteers*. 47th Annu Meet Am Coll Neuropsychopharmacol (Dec 7-11, Scottsdale) 2008, Abst 35.

9. Fowler, J.S. et al. *Reversible inhibitors of monoamine oxidase-A (RIMAs): Robust, reversible inhibition of human brain MAO-A by CX157*. Neuropsychopharmacology 2010, 35(3): 623.

10. *A study of CX157 (Tyrima) for the treatment of depression (CX157-200) (NCT00739908)*. ClinicalTrials.gov Web Site 2008, Oct 20.

11. *CeNeRx BioPharma announces positive phase I results in first human trial of third generation RIMA antidepressant*. CeNeRx BioPharma Press Release 2007, March 13.

12. *CeNeRx BioPharma announces successful completion of phase I clinical program for novel antidepressant agent Tyrima(TM)*. CeNeRx BioPharma Press Release 2008, Jan 16.

13. *CeNeRx BioPharma initiates human trials of RIMA antidepressant*. CeNeRx BioPharma Press Release 2007, Jan 30.

14. *CeNeRx completes USD 9 million financing and acquires rights to CXB-909 from Krenitsky*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2009, June 18.

15. *CeNeRx initiates phase II Tyrima trial in depression*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2008, Oct 21.

16. *CeNeRx secures funds for phase II trial of new CX-157 formulation for depression*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2010, Aug 16.

17. *CeNeRx to initiate phase II trial of Tyrima in depression in third quarter of 2008*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2008, July 24.

18. *Tyrima begins clinical testing for depression and anxiety*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2007, Feb 1.

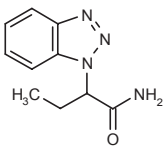
19. *Tyrima safe and well tolerated in phase I trial*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2007, March 15.

NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

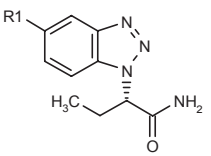
704213

2-(1*H*-Benzotriazol-1-yl)butyramide



C10H12N4O; Mol wt: 204.2285

ACTION – Benzotriazole derivative that showed anticonvulsant activity when orally administered to mice (ED_{50} = 38 mg/kg). Reported to be useful for the treatment of epilepsy, convulsions and tremor, among other CNS related disorders. Other representative compounds are:



Compound	R1	Formula
704216	Br	$C_{10}H_{11}BrN_4O$
704217	F	$C_{10}H_{11}FN_4O$

SOURCE – NeuroSearch.

REFERENCES

1. Nardi, A. et al. (NeuroSearch A/S) *Novel benzotriazole derivatives useful for the treatment of CNS disorders*. WO 2010081898.

3. Brot, E.C.A. et al. (CeNeRx BioPharma, Inc.) *Polymorphic form of fluoro-7-(2,2,2-trifluoroethoxy)phenoxathiin-10,10-dioxide*. US 2008009542, WO 2008008273.

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5. Asgharnejad, M. et al. *Results of a double-blind, placebo-controlled study of CX157 (TriRima), a reversible specific monoamine oxidase a inhibitor, in the treatment of major depressive disorder*. 27th World Congr CINP (June 6-10, Hong Kong) 2010, Abst 2.

6. Burch, D. et al. *Steady state pharmacokinetics and safety of CX157 (TriRima), a reversible specific monoamine oxidase an inhibitor*. 27th World Congr CINP (June 6-10, Hong Kong) 2010, Abst 5.

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9. Fowler, J.S. et al. *Reversible inhibitors of monoamine oxidase-A (RIMAs): Robust, reversible inhibition of human brain MAO-A by CX157*. Neuropsychopharmacology 2010, 35(3): 623.

10. *A study of CX157 (Tyrima) for the treatment of depression (CX157-200) (NCT00739908)*. ClinicalTrials.gov Web Site 2008, Oct 20.

11. *CeNeRx BioPharma announces positive phase I results in first human trial of third generation RIMA antidepressant*. CeNeRx BioPharma Press Release 2007, March 13.

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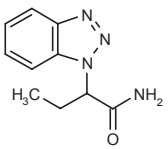
NEUROLOGIC DRUGS

ANTIEPILEPTIC DRUGS

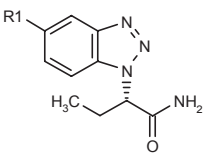
704213

2-(1*H*-Benzotriazol-1-yl)butyramide



C10H12N4O; Mol wt: 204.2285

ACTION – Benzotriazole derivative that showed anticonvulsant activity when orally administered to mice (ED_{50} = 38 mg/kg). Reported to be useful for the treatment of epilepsy, convulsions and tremor, among other CNS related disorders. Other representative compounds are:



Compound	R1	Formula
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704217	F	$C_{10}H_{11}FN_4O$

SOURCE – NeuroSearch.

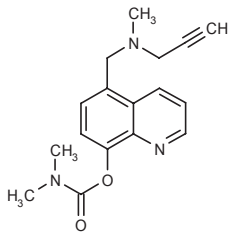
REFERENCES

1. Nardi, A. et al. (NeuroSearch A/S) *Novel benzotriazole derivatives useful for the treatment of CNS disorders*. WO 2010081898.

TREATMENT OF EXTRAPYRAMIDAL MOVEMENT DISORDERS

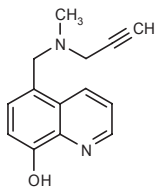
700772[2,12]

N,*N*-Dimethylcarbamic acid 5-[*N*-methyl-*N*-(2-propynyl)amino-methyl]quinolin-8-yl ester



C17H19N3O2; Mol wt: 297.3517

ACTION – Site-activated iron chelator that is activated to release **M-30**. Compound inhibited acetylcholinesterase and MAO-A with respective IC_{50} values of 0.52 and 0.0077 µM, with selectivity over butyrylcholinesterase and MAO-B (IC_{50} = 44.90 and 7.90 µM, respectively). Potentially useful for the treatment of Parkinson's disease and cancer.



M-30 [393832][1,3-14]: C14H14N2O

SOURCES – Rappaport Family Institute for Research in the Medical Sciences, Haifa (IL); Weizmann Institute of Science, Rehovot (IL).

REFERENCES

1. Warshawsky, A. et al. (Technion-Israel Institute of Technology;Yeda Research & Development Co. Ltd.) *Neuroprotective iron chelators and pharmaceutical compositions comprising them*. EP 1565185, JP 2006515599, US 2006234927, WO 2004041151.

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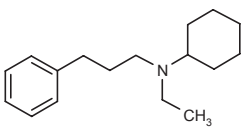
TREATMENT OF COGNITION DISORDERS

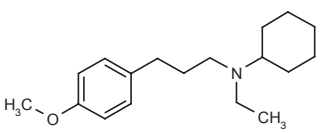
696431

N-Ethyl-*N*-(3-phenylpropyl)cyclohexylamine



C17H27N; Mol wt: 245.4030

ACTION – σ Receptor ligand that inhibited the binding of [^{3}H]-(+)-pentazocine to σ receptors expressed in membrane preparations from guinea pig whole brain (K_i = 8.7 nM). Compound promoted neurite outgrowth by 59.9 and 61.7%, respectively, at 0.3 and 1 µM, in rat cerebral cortex nerve cells. Reported to be useful for the treatment of central nervous system disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, dementia, neuropathy and motor dysfunction. Another representative compound is:



704973: C18H29NO

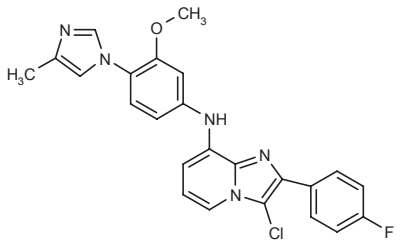
SOURCE – M's Science.

REFERENCES

1. Mita, S. and Kobayashi, N. (M's Science Corp.) *Cyclohexylamine derivative containing phenyl group, and therapeutic agent for diseases accompanied by central nervous system disorders*. WO 2010050435.

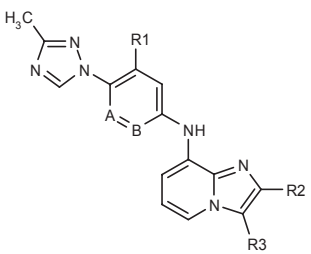
700294

3-Chloro-2-(4-fluorophenyl)-*N*-[3-methoxy-4-(4-methyl-1*H*-imidazol-1-yl)phenyl]imidazo[1,2-*a*]pyridin-8-amine

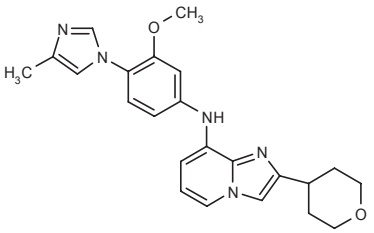


C24H19ClFN5O; Mol wt: 447.8920

ACTION – γ-Secretase modulator that selectively inhibited the production of β-amyloid peptide $A\beta_{42}$ and total Aβ expressed in human neuroblastoma SK-N-BE(2) cells (IC_{50} = 0.065 and > 3 μM, respectively). A single oral dose to nontransgenic mice showed marked reduction in $A\beta_{42}$ (100%) and total Aβ (106%) peptide levels in brain homogenates. Reported to be useful for the treatment of Alzheimer's disease. Further applications include traumatic brain injury, mild cognitive impairment, senility, dementia with Lewy bodies, cerebral amyloid angiopathy, multi-infarct dementia, Down's syndrome, dementia associated with Parkinson's disease and β-amyloid. Related compounds include:



Compound	R1	R2	R3	A	B	Formula
700282	H	4-F-2-Me-Ph	H	N	CH	$C_{22}H_{18}FN_7$
700283	OMe	2-Me-Ph	H	CH	CH	$C_{24}H_{22}N_6O$
700284	H	2-Me-Ph	H	N	CH	$C_{22}H_{19}N_7$
700285	H	2-Cl-Ph	Me	CH	N	$C_{22}H_{18}ClN_7$
700287	H	2-Me-Ph	H	CH	CH	$C_{23}H_{20}N_6$
700291	F	2-Me-5-CF3-Ph	H	CH	CH	$C_{24}H_{18}F_4N_6$
700293	F	2-Me-5-MeO-Ph	H	CH	CH	$C_{24}H_{21}FN_6O$



700290: C23H25N5O2

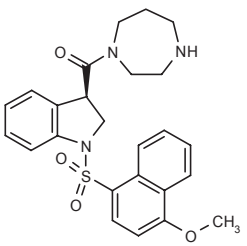
SOURCE – Ortho-McNeil-Janssen.

REFERENCES

1. Gijsen, H.J.M. et al. (Ortho-McNeil-Janssen Pharmaceuticals, Inc.) *Substituted bicyclic imidazole derivatives as gamma secretase modulators*. WO 2010070008.

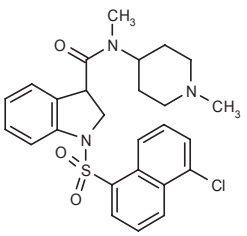
700700

1-[1-(4-Methoxynaphthalen-1-ylsulfonyl)-2,3-dihydro-1*H*-indole-3(*R*)-yl]-1-(perhydro-1,4-diazepin-1-yl)methanone



C25H27N3O4S; Mol wt: 465.5650

ACTION – 5-HT6 receptor antagonist that displayed a pK_i of 9.2 in binding assays and a pEC_{50} of 7.2 in functional assays with selectivity (> 100-fold) over other 5-HT receptor subtypes. Compound displayed an oral bioavailability of 23.5% in rats. Potentially useful for the treatment of cognitive disorders such as Alzheimer's disease and schizophrenia. Another representative compound is:



700701: C26H28ClN3O3S

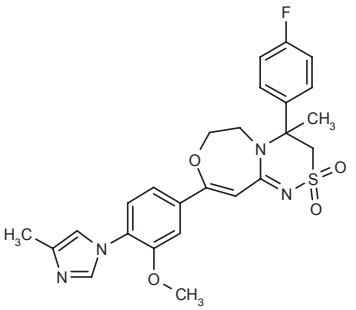
SOURCE – Merck & Co.

REFERENCES

1. Reid, M. et al. *The discovery and SAR of indoline-3-carboxamides--a new series of 5-HT6 antagonists.* Bioorg Med Chem Lett 2010, 20(12): 3713.

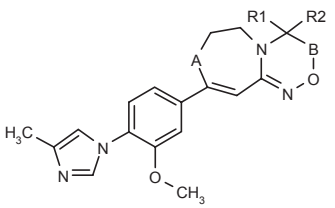
701378

4-(4-Fluorophenyl)-9-[3-methoxy-4-(4-methyl-1*H*-imidazol-1-yl)phenyl]-4-methyl-3,4,6,7-tetrahydro[1,2,4]thiadiazino[4,3-*d*]-[1,4]oxazepine 2,2-dioxide

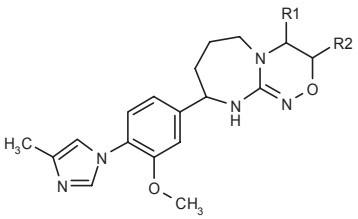


C25H25FN4O4S; Mol wt: 496.5540

ACTION – γ-Secretase modulator reported to be useful for the treatment of neurodegenerative diseases such as Alzheimer's disease, Down's syndrome and other diseases related to amyloid protein deposition. Related compounds include:



Compound	R1	R2	A	B	Formula
701381	4-F-Ph	Me	O	CH2	$C_{25}H_{25}FN_4O_3$
701384	4-F-Ph	Me	CH2	bond	$C_{25}H_{25}FN_4O_2$
701395	CH2Ph	H	CH2	CH2	$C_{26}H_{28}N_4O_2$



Compound	R1	R2	Formula
701386	3,4,5-(F)3-Ph	H	$C_{24}H_{24}F_3N_5O_2$
701388	H	3,4,5-(F)3-Ph	$C_{24}H_{24}F_3N_5O_2$
701391	Me	3,4,5-(F)3-Ph	$C_{25}H_{26}F_3N_5O_2$
701392	3,5-(F)2-PhCH2	H	$C_{25}H_{27}F_2N_5O_2$

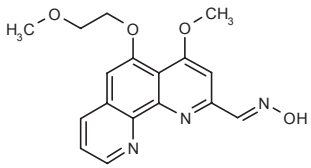
SOURCE – Merck & Co.

REFERENCES

1. Asberom, T. et al. (Schering Corp.) *gamma Secretase modulators*. WO 2010075204.

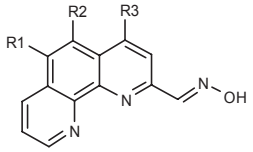
701514

4-Methoxy-5-(2-methoxyethoxy)-1,10-phenanthroline-2-carbaldehyde oxime

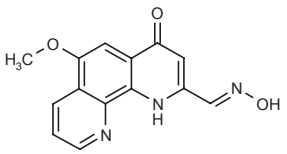


C17H17N3O4; Mol wt: 327.3346

ACTION – β-Amyloid (Aβ) inhibitor that at 1000 μM was nontoxic to neuroblastoma SH-SY5Y cells and protected against hydrogen peroxide-, 6-OHDA- and $A\beta_{25-35}$-induced toxicity at concentrations of 0.005, 0.5 and 5 μM, respectively. Compound (0.1 μM) inhibited the production of $A\beta_{1-40}$ in an APP-transfected cell line. Reported to be useful for the treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's disease, as well as hematological diseases, particularly anemia, thalassemia and sickle cell disease. Related compounds include:



Compound	R1	R2	R3	Formula
701515	H	OMe	SMe	$C_{15}H_{13}N_3O_2S$
701516	H	F	OMe	$C_{14}H_{10}FN_3O_2$
701517	H	Me	SMe	$C_{15}H_{13}N_3OS$
701518	OMe	H	SMe	$C_{15}H_{13}N_3O_2S$



701519: C14H11N3O3

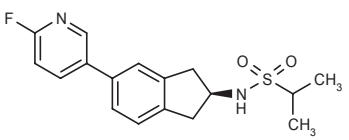
SOURCE – Noscira.

REFERENCES

1. Medina Padilla, M. et al. (Noscira, SA) *Triple substituted phenanthroline derivatives for the treatment of neurodegenerative or heamatological diseases or conditions*. EP 2196466, WO 2010066832.

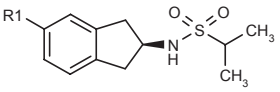
701624[1-3]

N-[5-(6-Fluoropyridin-3-yl)-2,3-dihydro-1*H*-inden-2(*S*)-yl]propane-2-sulfonamide



C17H19FN2O2S; Mol wt: 334.4080

ACTION – Glutamate receptor GluR2 positive allosteric modulator that activated human GluR2 receptors expressed in HEK-293 cells with a pEC_{50} of 5.0 in a calcium influx assay. Compound was effective in behavioral models of cognition and the novel object recognition model (MED = 0.3 mg/kg p.o.) in rats. Oral bioavailability was 61%. It was safe and well tolerated in healthy volunteers in a phase I trial. Potentially useful for the treatment of schizophrenia, Alzheimer's disease, Parkinson's disease and mood disorders. Other related compounds are:



Compound	R1	Formula
701626[1,3]	6-Me-3-Pyr	$C_{18}H_{22}N_2O_2S$
701627[1,3]	5-F-2-Pyr	$C_{17}H_{19}FN_2O_2S$

SOURCE – GlaxoSmithKline.

REFERENCES

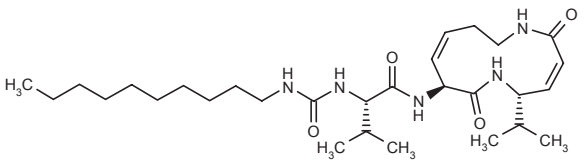
1. Bradley, D.M. et al. (GlaxoSmithKline plc) *Compounds which potentiate glutamate receptor and uses thereof in medicine*. EP 1781614, EP 1944289, JP 2008509180, US 2007161638, US 7572819, US 7618969, WO 2006015828.

2. Bradley, D.M. et al. (GlaxoSmithKline plc) *Compounds which potentiate glutamate receptor and uses thereof in medicine*. US 2008194648.

3. Ward, S.E. et al. *Discovery of N-[(2S)-5-(6-Fluoro-3-pyridinyl)-2,3-dihydro-1H-inden-2-yl]-2-propanesulfonamide, a novel clinical AMPA receptor positive modulator*. J Med Chem 2010, 53(15): 5801.

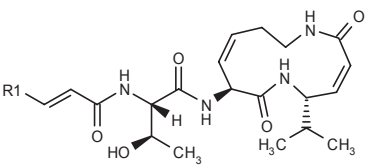
704209

N^2-(*N*-Decylcarbamoyl)-*N*-[5(S)-isopropyl-2,7-dioxo-1,6-diazacyclododeca-3,9-dien-8(*S*)-yl]-L-valinamide

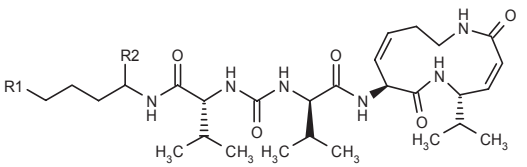


C29H51N5O4; Mol wt: 533.7463

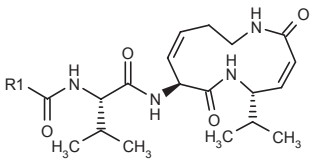
ACTION – Tau aggregation inhibitor that inhibited chymotryptic, tryptic and caspase-like proteasome activities (K_i < 20, 20-100 and > 100 nM, respectively). Reported to be useful for the treatment of neurodegenerative disorders, cancer, polyarthritis, psoriasis, allograft rejection, transplant rejection, graft versus host disease and cardiovascular disorders. Other representative compounds are:



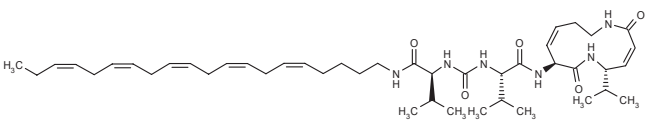
Compound	R1	Formula
704187	CH=CHC7H15	$C_{29}H_{46}N_4O_5$
704195	CH2CH=CHC6H13	$C_{29}H_{46}N_4O_5$



Compound	R1	R2	Formula
704196	CH(Me)SOMe	Et	$C_{33}H_{58}N_6O_6S$
704199	CO2Pr	H	$C_{32}H_{54}N_6O_7$



Compound	R1	Formula
704205	1-pyrrolidinyl	$C_{23}H_{37}N_5O_4$
704207	NHPh	$C_{25}H_{35}N_5O_4$



704202: C44H70N6O5

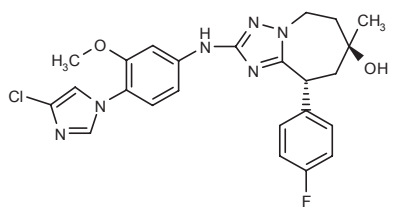
SOURCE – Max-Planck-Gesellschaft, Munich (DE).

REFERENCES

1. Kaiser, M. and Clerc, J. (Max-Planck-Gesellschaft zur Förderung der Wissenschaften eV) *Derivatives of syringolin A*. EP 2210881, WO 2010081731.

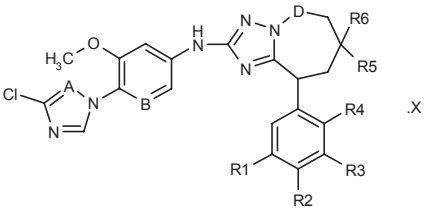
704335

2-[4-(4-Chloro-1*H*-imidazol-1-yl)-3-methoxyphenylamino]-9(*R*)-(4-fluorophenyl)-7(*S*)-methyl-6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[1,5-*a*]-azepin-7-ol



C24H24ClFN6O2; Mol wt: 482.9380

ACTION – β-Amyloid production inhibitor (IC_{50} = 2 nM in NCl-H4 cells), reported to be useful for the treatment of Alzheimer's disease. Further applications include Down's syndrome, mild cognitive impairment, cerebral amyloid angiopathy, Lewy body dementia, amyotrophic lateral sclerosis, inclusion body myositis, age-related macular degeneration and cancer. Other representative compounds are:



Compound	R1=R3	R2	R4	R5	R6	A	B	D	Isomer	X	Formula
704336	H	Cl	Cl	H	H	CH	CH	bond		TFA	$C_{24}H_{20}Cl_3F_3N_6O_3$
704338	H	F	H	H	H	N	CH	CH2		TFA	$C_{24}H_{22}ClF_4N_7O_3$
704340	F	F	H	H	H	CH	CH	CH2	S		$C_{23}H_{20}ClF_3N_6O$
704341	H	F	H	H	H	CH	N	CH2			$C_{22}H_{21}ClFN_7O$
704343	H	OCH2CF3	H	H	H	CH	CH	CH2	S		$C_{25}H_{24}ClF_3N_6O_2$
704344	H	F	H	-CH2-		CH	CH	CH2	S		$C_{24}H_{22}ClFN_6O$

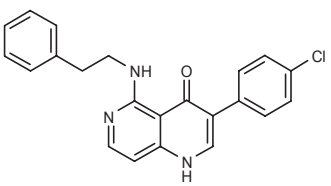
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Marcin, L.R. et al. (Bristol-Myers Squibb Co.) *Bicyclic compounds for the reduction of β-amyloid production*. WO 2010083141.

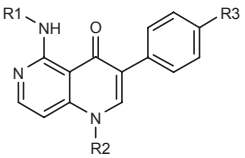
704482

3-(4-Chlorophenyl)-5-(2-phenylethylamino)-1,6-naphthyridin-4(1*H*)-one



C22H18ClN3O; Mol wt: 375.8510

ACTION – Nicotinic acetylcholine α7 modulator reported to be useful for the treatment of cognitive disorders such as mild cognitive impairment, age-related cognitive decline, senile dementia and Alzheimer's disease, among other disorders. Related compounds include:



Compound	R1	R2	R3	Formula
704483	CH2CH2Ph	Me	Cl	$C_{23}H_{20}ClN_3O$
704484	4-F-Ph	H	Cl	$C_{20}H_{13}ClFN_3O$
704485	CH2Ph	H	OEt	$C_{23}H_{21}N_3O_2$
704486	CH2CH2Ph	H	Me	$C_{23}H_{21}N_3O$
704488	Pr	Me	OEt	$C_{20}H_{23}N_3O_2$
704489	Ph	Et	OMe	$C_{23}H_{21}N_3O_2$
704492	4-Cl-Ph	H	F	$C_{20}H_{13}ClFN_3O$

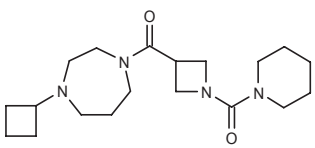
SOURCE – Anvyl.

REFERENCES

1. Kanner, R.C. (Anvyl, LLC) *α7 Nicotinic acetylcholine receptor allosteric modulators, their derivatives and uses thereof*. US 2010190819, WO 2010083444.

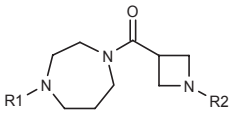
705160

1-(4-Cyclobutylperhydro-1,4-diazepin-1-yl)-1-[1-(piperidin-1-ylcarbonyl)azetidin-3-yl]methanone



C19H32N4O2; Mol wt: 348.4830

ACTION – Histamine H3 receptor antagonist that inhibited histamine receptor agonist-induced intracellular free cAMP levels decrease in CHO-K1 cells (IC_{50} < 50 nM). Potentially useful for the treatment of Alzheimer's disease, Parkinson's disease, attention deficit hyperactivity disorder, schizophrenia, idiopathic hypersomnia, narcolepsy, obesity, neuropathic pain and multiple sclerosis. Further applications include disorders affecting energy homeostasis, cardiovascular disorders, gastrointestinal disorders, vestibular dysfunction, substance abuse, nasal congestion, allergic rhinitis and asthma. Related compounds include:



Compound	R1	R2	Formula
705164	cyclobutyl	6-(1,2,4-triazol-1-yl)-3-Pyr-CO	$C_{21}H_{27}N_7O_2$
705165	cyclobutyl	cyclopentyl-CH2SO2	$C_{19}H_{33}N_3O_3S$
705167	cyclobutyl	4-CN-PhCH2CO	$C_{22}H_{28}N_4O_2$
705169	cyclobutyl	3-(2-Me-4-thiazolyl)-PhCO	$C_{24}H_{30}N_4O_2S$
705172	cyclobutyl	4-THP-CH2NHCO	$C_{20}H_{34}N_4O_3$
705176	cyclobutyl	6-Me-3-Pyr-OCO	$C_{20}H_{28}N_4O_3$
705179	cyclohexyl	6-Me-3-Pyr-CO	$C_{22}H_{32}N_4O_2$

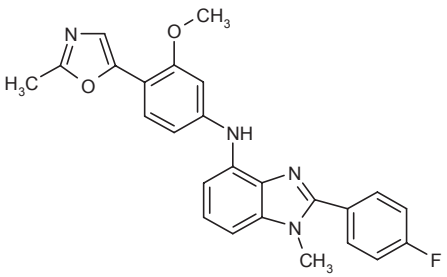
SOURCE – Evotec Neurosciences.

REFERENCES

1. Davenport, A.J. et al. (Evotec Neurosciences GmbH) *Azetidines as histamine H3 receptor antagonists*. WO 2010086403.

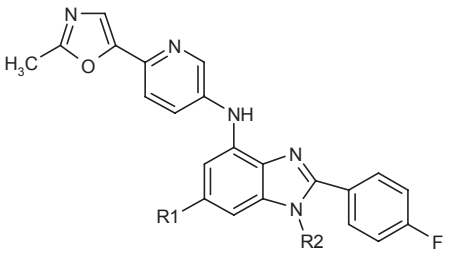
705832

2-(4-Fluorophenyl)-*N*-[3-methoxy-4-(2-methyloxazol-5-yl)phenyl]-1-methyl-1*H*-benzimidazol-4-amine



C25H21FN4O2; Mol wt: 428.4582

ACTION – γ-Secretase modulator that inhibited the production of β-amyloid peptide $Aβ_{42}$ and total Aβ expressed in SK-N-BE(2) cells (IC_{50} = 0.011 and > 3 μM, respectively). A single oral dose to non-transgenic mice showed marked reduction in $Aβ_{42}$ (58%) and total Aβ (95%) peptide levels in brain homogenates. Reported to be useful for the treatment of Alzheimer's disease. Further applications include traumatic brain injury, mild cognitive impairment, senility, dementia with Lewy bodies, cerebral amyloid angiopathy, multi-infarct dementia, Down's syndrome, dementia associated with Parkinson's disease and β-amyloid. Related compounds include:



Compound	R1	R2	Formula
705828	F	Me	$C_{23}H_{17}F_2N_5O$
705831	H	i-Pr	$C_{25}H_{22}FN_5O$

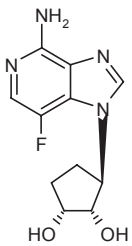
SOURCE – Ortho-McNeil-Janssen.

REFERENCES

1. Gijsen, H.J.M. et al. (Ortho-McNeil-Janssen Pharmaceuticals, Inc.) *Novel substituted bicyclic heterocyclic compounds as gamma secretase modulators*. WO 2010089292.

706263

3(*R*)-(4-Amino-7-fluoro-1*H*-imidazo[4,5-*c*]pyridin-1-yl)cyclopentane-1(*R*),2(*S*)-diol



C11H13FN4O2; Mol wt: 252.2449

ACTION – Adenosylhomocysteinase inhibitor (IC_{50} = 40 and 1.6 nM, respectively, in enzymatic and cellular assays). Compound exhibited an oral bioavailability of 86.5 and 160%, respectively, in rats and dogs. Potentially useful for the treatment of Alzheimer's disease.

SOURCE – Merck & Co.

REFERENCES

1. Converso, A. et al. (Merck & Co., Inc.) *AHCY hydrolase inhibitors for treatment of hyper homocysteinemia*. WO 2010027935.

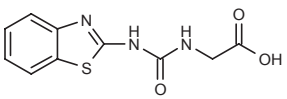
2. Hartingh, T.J. et al. *Novel inhibitors of AHCY for the treatment of Alzheimer's disease*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 43.

KHG-25967

701715

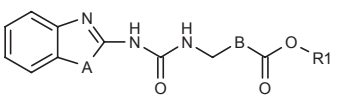
N-[*N*-(2-Benzothiazolyl)carbamoyl]glycine

2-[3-(2-Benzothiazolyl)ureido]acetic acid



C10H9N3O3S; Mol wt: 251.2620

ACTION – Inhibitor β-amyloid (Aβ)-induced neurotoxicity (50 nM) that blocked Aβ by 83% in microglia BV-2 cells in cell viability assays. Compound (50 nM) reduced levels of lipopolysaccharide (LPS)-induced phospho-MAP kinase 1, MAP kinase 3 and caspase-3 by 90, 70 and 93%, respectively, and suppressed IL-1β and TNF-α by 70 and 61%, respectively. At 10-20 mg/kg/day p.o. for 2 weeks it decreased TNF-α and IL-1β levels in C57BL6 mice by 42 and 55%, respectively. Reported to be useful for the treatment of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, stroke, amyloidosis, Pick's disease, Lou Gehrig's disease, Huntington's disease and Creutzfeld-Jakob diseases. Related compounds include:



Compound	R1	A	B	Formula
KHG-26025 [701722]	H	S	-(CH2)2-	$C_{12}H_{13}N_3O_3S$
KHG-26026 [701728]	H	S	-CH2-	$C_{11}H_{11}N_3O_3S$
KHG-26029 [701734]	Et	N(Me)	bond	$C_{13}H_{16}N_4O_3$
KHG-26030 [701737]	Et	N(Me)	-CH2-	$C_{14}H_{18}N_4O_3$

SOURCE – Korea Institute of Science and Technology, Seoul (KR).

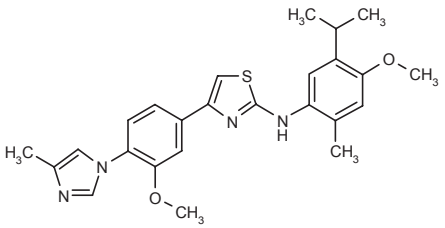
REFERENCES

1. Hahn, H.-G. et al. (Korea Institute of Science and Technology) *Benzoarylureido compounds, and composition for prevention or treatment of neurodegenerative brain disease containing the same*. WO 2010077068.

NGP-328

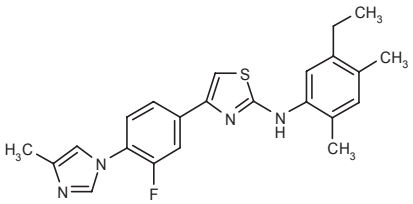
706409

N-(5-Isopropyl-4-methoxy-2-methylphenyl)-4-[3-methoxy-4-(4-methyl-1*H*-imidazol-1-yl)phenyl]thiazol-2-amine



C25H28N4O2S; Mol wt: 448.5800

ACTION – γ-Secretase modulator that selectively inhibited the production of β-amyloid peptide $A\beta_{1-42}$, and increased $A\beta_{38}$ in plasma, cerebrospinal fluid and brain. Potentially useful for the treatment of neurodegenerative diseases such as Alzheimer's disease. Another representative compound is:



NGP-555 [706404]: C23H23FN4S

SOURCE – NeuroGenetic Pharmaceuticals.

REFERENCES

1. Cheng, S. et al. (NeuroGenetic Pharmaceuticals, Inc.) *Compounds and uses thereof in modulating amyloid beta*. EP 1628666, JP 2007504282, US 2005070538, US 7244739, WO 2004110350.

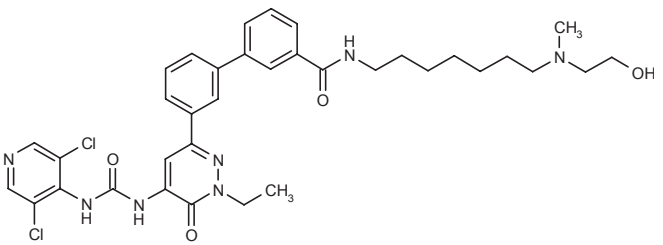
2. Cheng, S. et al. *2-Aminothiazoles derivatives as potent gamma-secretase modulators*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 1.

RESPIRATORY DRUGS

ASTHMA AND COPD THERAPY

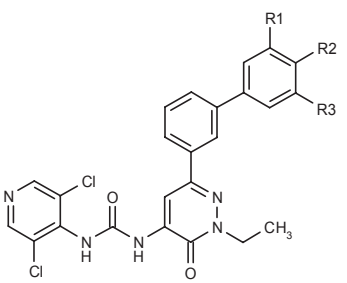
701559

3'-[5-[3-(3,5-Dichloropyridin-4-yl)ureido]-1-ethyl-6-oxo-1,6-dihydropyridazin-3-yl]-*N*-[7-[*N*-(2-hydroxyethyl)-*N*-methylamino]-heptyl]biphenyl-3-carboxamide



C35H41Cl2N7O4; Mol wt: 694.6510

ACTION – Phosphodiesterase PDE4 inhibitor (IC_{50} = 0.031 nM), described as useful for the treatment of asthma, chronic obstructive pulmonary disease, allergic rhinitis, rheumatoid arthritis, multiple sclerosis, atopic dermatitis, psoriasis and inflammatory bowel disease. Related compounds include:

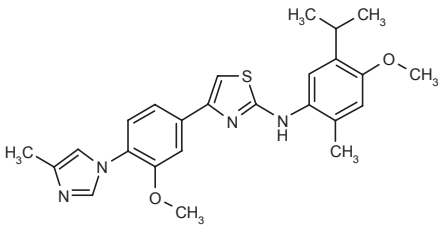


Compound	R1	R2	R3	Formula
701565	H	H	CONHCH2CH2N(Me)2	$C_{29}H_{29}Cl_2N_7O_3$
701568	H	CO2H	H	$C_{25}H_{19}Cl_2N_5O_4$
701569	H	1-Pip-CH2CH2NHCOCH2	H	$C_{33}H_{35}Cl_2N_7O_3$
701572	H	H	4-morpholinyl--CH2CH2NHCOCH2	$C_{32}H_{33}Cl_2N_7O_4$
701575	H	CH2CONH(CH2)7-N(Me)CH2CH2OH	H	$C_{36}H_{43}Cl_2N_7O_4$
701577	OH	H	CONH(CH2)7-N(Me)CH2CH2OH	$C_{35}H_{41}Cl_2N_7O_5$
701578	OH	H	cyclopropyl-NHCO	$C_{28}H_{24}Cl_2N_6O_4$

NGP-328

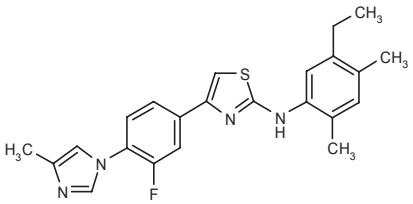
706409

N-(5-Isopropyl-4-methoxy-2-methylphenyl)-4-[3-methoxy-4-(4-methyl-1*H*-imidazol-1-yl)phenyl]thiazol-2-amine



C25H28N4O2S; Mol wt: 448.5800

ACTION – γ-Secretase modulator that selectively inhibited the production of β-amyloid peptide $A\beta_{1-42}$, and increased $A\beta_{38}$ in plasma, cerebrospinal fluid and brain. Potentially useful for the treatment of neurodegenerative diseases such as Alzheimer's disease. Another representative compound is:



NGP-555 [706404]: C23H23FN4S

SOURCE – NeuroGenetic Pharmaceuticals.

REFERENCES

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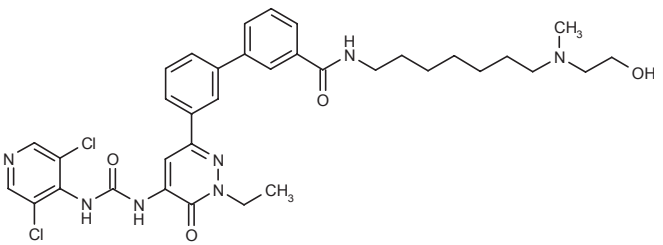
2. Cheng, S. et al. *2-Aminothiazoles derivatives as potent gamma-secretase modulators*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 1.

RESPIRATORY DRUGS

ASTHMA AND COPD THERAPY

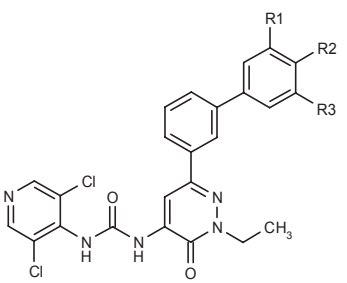
701559

3'-[5-[3-(3,5-Dichloropyridin-4-yl)ureido]-1-ethyl-6-oxo-1,6-dihydropyridazin-3-yl]-*N*-[7-[*N*-(2-hydroxyethyl)-*N*-methylamino]-heptyl]biphenyl-3-carboxamide



C35H41Cl2N7O4; Mol wt: 694.6510

ACTION – Phosphodiesterase PDE4 inhibitor (IC_{50} = 0.031 nM), described as useful for the treatment of asthma, chronic obstructive pulmonary disease, allergic rhinitis, rheumatoid arthritis, multiple sclerosis, atopic dermatitis, psoriasis and inflammatory bowel disease. Related compounds include:



Compound	R1	R2	R3	Formula
701565	H	H	CONHCH2CH2N(Me)2	$C_{29}H_{29}Cl_2N_7O_3$
701568	H	CO2H	H	$C_{25}H_{19}Cl_2N_5O_4$
701569	H	1-Pip-CH2CH2NHCOCH2	H	$C_{33}H_{35}Cl_2N_7O_3$
701572	H	H	4-morpholinyl--CH2CH2NHCOCH2	$C_{32}H_{33}Cl_2N_7O_4$
701575	H	CH2CONH(CH2)7-N(Me)CH2CH2OH	H	$C_{36}H_{43}Cl_2N_7O_4$
701577	OH	H	CONH(CH2)7-N(Me)CH2CH2OH	$C_{35}H_{41}Cl_2N_7O_5$
701578	OH	H	cyclopropyl-NHCO	$C_{28}H_{24}Cl_2N_6O_4$

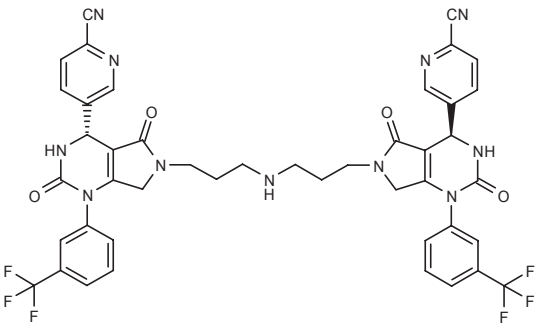
SOURCE – Almirall.

REFERENCES

1. Gracia Ferrer, J. et al. (Laboratorios Almirall, SA) *(3-Oxo)pyridazin-4-ylurea derivatives as PDE4 inhibitors*. EP 2196465, WO 2010069504.

705029

5,5'-Iminobis(propane-1,3-diyl)bis[1-[3-(trifluoromethyl)phenyl]-2,5-dioxo-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo[3,4-*d*]pyrimidin-6,4(*R*)-diyl]bis(pyridine-2-carbonitrile)



C44H35F6N11O4; Mol wt: 895.8104

ACTION – Human neutrophil elastase inhibitor (IC_{50} = 8.4 nM) that reduced lung hemorrhage by 88% in rats at 100 mg/kg intratracheally. Potentially useful for the treatment of respiratory diseases such as chronic obstructive pulmonary diseases, acute respiratory distress syndrome, cystic fibrosis, pneumonia, lung fibrosis, asthma, pulmonary emphysema and rhinitis.

SOURCE – Pulmagen Therapeutics.

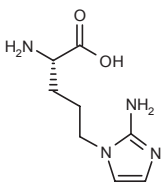
REFERENCES

1. Edwards, C. et al. (Pulmagen Therapeutics) *Dimeric pyrrolopyrimidinedione and its use in therapy of respiratory diseases*. WO 2010086638.

A1P

698475

5-(2-Amino-1*H*-imidazol-1-yl)-L-norvaline



C8H14N4O2; Mol wt: 198.2224

ACTION – Arginase-1 inhibitor (K_i = 4 μM and K_d = 2 μM for human enzyme) that significantly attenuated airways hyperresponsiveness in a murine model of allergic airways inflammation at 80 μg/g by nebulization. Potentially useful for the treatment of allergic asthma.

SOURCES – University of Pennsylvania, Philadelphia, PA (US); University of Toronto, Toronto, ON (CA).

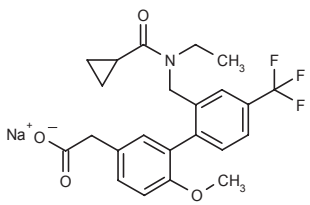
REFERENCES

1. Ilies, M. et al. *2-Aminoimidazole amino acids as inhibitors of the binuclear manganese metalloenzyme human arginase I*. J Med Chem 2010, 53(10): 4266.

AM-156

695278

2-[2'-[*N*-(Cyclopropylcarbonyl)-*N*-ethylaminomethyl]-6-methoxy-4'-(trifluoromethyl)biphenyl-3-yl]acetic acid sodium salt



C23H23F3NNaO4; Mol wt: 457.4180

ACTION – Prostanoid DP2 receptor antagonist (IC_{50} = 13.5 nM for human receptor binding) with selectivity over DP1, TP and IP receptors (IC_{50} = 58, 105 and 123 μM, respectively). It inhibited [^{3}H]-PGD_2-induced eosinophil shape change in human blood (IC_{50} = 6.8 nM). Compound increased total bronchoalveolar lavage fluid leukocytes with an MED of 10 mg/kg p.o. in an acute model of cigarette smoke exposure, inhibited neutrophil and lymphocyte trafficking to airways and inhibited pulmonary inflammation and mucus hypersecretion induced by chronic inhalation of house dust in mice. Potentially useful for the treatment of allergic asthma, chronic obstructive pulmonary diseases and allergic rhinitis.

SOURCE – Amira Pharmaceuticals.

REFERENCES

1. Hutchinson, J.H. et al. (Amira Pharmaceuticals, Inc.) *N,N-Disubstituted aminoalkylbiphenyl antagonists of prostaglandin D2 receptors*. GB 2460597, US 2009197959, WO 2009099901, WO 2009099902.

2. Stebbins, K.J. et al. *Pharmacological blockade of the DP2 receptor inhibits cigarette smoke-induced inflammation, mucus cell metaplasia, and epithelial hyperplasia in the mouse lung*. J Pharmacol Exp Ther 2010, 332(3): 764.

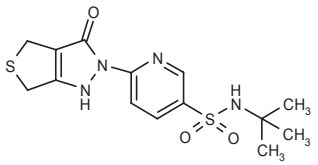
3. Stebbins, K.J. et al. *Therapeutic efficacy of AM156, a novel prostanoid DP2 receptor antagonist, in murine models of allergic rhinitis and house dust mite-induced pulmonary inflammation*. Eur J Pharmacol 2010, 638(1-3): 142.

CARDIOVASCULAR DRUGS

TREATMENT OF HYPERTENSION

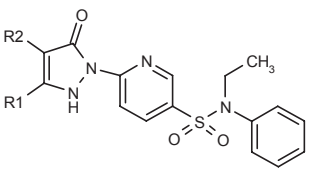
701739

N-tert-Butyl-6-(3-oxo-2,3,4,6-tetrahydro-1*H*-thieno[3,4-*c*]pyrazol-2-yl)pyridine-3-sulfonamide



C14H18N4O3S2; Mol wt: 354.4480

ACTION – Hypoxia-inducible factor HIF-1α activator with an EC_{50} of 4.4 μM in HEK cells that enhanced the activity of vascular endothelial growth factor and erythropoietin receptor in hepatocarcinoma Hep 3B cells (EC_{50} = 0.4 and 0.5 μM, respectively). Reported to be useful for the treatment of hypertension, heart failure, diabetes and anemia. Further applications include angina pectoris, myocardial infarction, atherosclerosis, ischemic stroke, pulmonary hypertension and diseases caused by partial or total vascular occlusion. Related compounds include:



Compound	R1	R2	Formula
701741	-CH2CH2CH2S-		$C_{19}H_{20}N_4O_3S_2$
701742	-CH2SCH2-		$C_{18}H_{18}N_4O_3S_2$

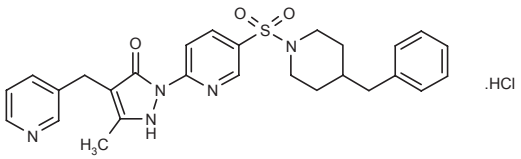
SOURCE – sanofi-aventis.

REFERENCES

1. Altenburger, J.-M. et al. (sanofi-aventis) *Derivatives of 2-pyridin-2-yl-pyrazol-3(2H)-one, preparation and therapeutic use thereof*. FR 2940652, WO 2010076525.

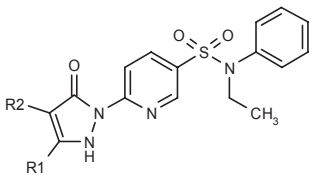
701753

2-[5-(4-Benzylpiperidin-1-ylsulfonyl)pyridin-2-yl]-5-methyl-4-(pyridin-3-ylmethyl)-2,3-dihydro-1*H*-pyrazol-3-one hydrochloride



C27H30ClN5O3S; Mol wt: 540.0770

ACTION – Hypoxia-inducible factor HIF-1α activator with an EC_{50} of 2 μM in HEK cells that enhanced the activity of vascular endothelial growth factor and erythropoietin receptor in hepatocarcinoma Hep 3B cells (EC_{50} = 0.2 μM). Reported to be useful for the treatment of hypertension, heart failure, diabetes, anemia and ischemic disorders. Further applications include angina pectoris, myocardial infarction, atherosclerosis, ischemic stroke, pulmonary hypertension and diseases caused by partial or total vascular occlusion. Related compounds include:



Compound	R1	R2	Formula
701754	Pr	CH2Ph	$C_{26}H_{28}N_4O_3S$
701755	Me	4-MeO-PhCH2	$C_{25}H_{26}N_4O_4S$
701756	Me	2-CF3-PhCH2	$C_{25}H_{23}F_3N_4O_3S$
701757	i-Bu	CH2Ph	$C_{27}H_{30}N_4O_3S$
701759	Me	(CH2)3Ph	$C_{26}H_{28}N_4O_3S$
701761	H	CH2Ph	$C_{23}H_{22}N_4O_3S$

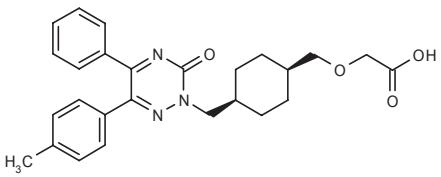
SOURCE – sanofi-aventis.

REFERENCES

1. Altenburger, J.-M. et al. (sanofi-aventis) *Derivatives of 2-pyridin-2-yl-pyrazol-3(2H)-one, preparation and therapeutic use thereof as HIF activators*. FR 2940651, WO 2010076524.

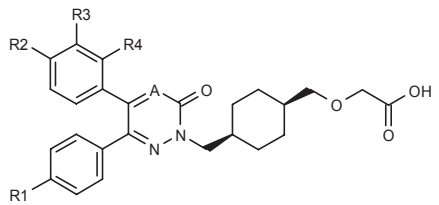
702046

cis-2-[4-[6-(4-Methylphenyl)-3-oxo-5-phenyl-2,3-dihydro-1,2,4-triazin-2-ylmethyl]cyclohexylmethoxy]acetic acid



C26H29N3O4; Mol wt: 447.5262

ACTION – Prostanoid IP1 receptor agonist that reduced monocrotaline-induced pulmonary arterial hypertension in male Wistar rats at 30 mg/kg p.o. Described as useful for the treatment of pulmonary arterial hypertension and related conditions such as platelet aggregation, myocardial infarction, restenosis, atherosclerosis, diabetes, chronic obstructive pulmonary disease, asthma and stroke, among others. Related compounds include:



Compound	R1	R2	R3	R4	A	Formula
702047	H	H	Cl	F	CH	$C_{26}H_{26}ClFN_2O_4$
702048	Me	Me	H	H	N	$C_{27}H_{31}N_3O_4$
702050	H	H	Cl	H	N	$C_{25}H_{26}ClN_3O_4$
702051	OMe	H	H	H	N	$C_{26}H_{29}N_3O_5$

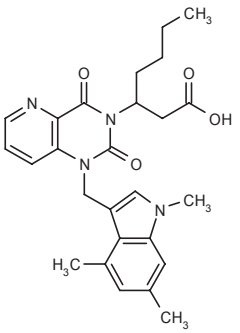
SOURCE – Arena.

REFERENCES

1. Tran, T.-A. et al. (Arena Pharmaceuticals, Inc.) *Modulators of the prostacyclin (PGI2) receptor useful for the treatment of disorders related thereto*. WO 2010077275.

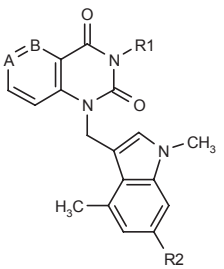
705258

3-[2,4-Dioxo-1-(1,4,6-trimethyl-1*H*-indol-3-ylmethyl)-1,2,3,4-tetrahydropyrido[3,2-*d*]pyrimidin-3-yl]heptanoic acid



C26H30N4O4; Mol wt: 462.5408

ACTION – Chymase inhibitor (IC_{50} = 0.3 nM) claimed for use in the treatment of systolic, resistant and pulmonary hypertension, and heart failure, myocardial infarction, reperfusion injury, hypertrophic cardiomyopathy, aneurysm, angina, restenosis, asthma, chronic obstructive pulmonary disease, pulmonary inflammation, renal disorders and stroke, among other disorders. Other representative compounds are:



Compound	R1	R2	A	B	Formula
705264	(R)-CH(Bu)CO2H	H	N	CH	$C_{24}H_{26}N_4O_4$
705266	CH(cyclopropyl)CH2CO2H	Me	CH	N	$C_{25}H_{26}N_4O_4$
705268	(R)-CH(Et)CH2CO2H	Me	CH	N	$C_{24}H_{26}N_4O_4$
705270	(R)-CH(Et)CH2CO2H	Me	N	CH	$C_{24}H_{26}N_4O_4$
705271	CH(Bu)CH2CO2H	H	CH	N	$C_{25}H_{28}N_4O_4$
705273	CH(Pr)CH2CO2H	H	CH	N	$C_{24}H_{26}N_4O_4$

SOURCE – Boehringer Ingelheim.

REFERENCES

1. Guo, X. et al. (Boehringer Ingelheim Pharma GmbH & Co. KG) *Azaquinazolinediones useful as chymase inhibitors*. WO 2010088195.

CANDESARTAN CILEXETIL/AMLODIPINE BESYLATE

656334

Combination of candesartan cilexetil and amlodipine besylate

ACTION – Angiotensin AT2 receptor antagonist/calcium channel blocker.

INDICATION – Treatment of hypertension.

PRESENTATION – Tablets, 8 mg/2.5 mg & 8 mg/5 mg candesartan cilexetil/amlodipine.

PROPRIETARY NAME – Unisia (JP).

SOURCE – Takeda.

REFERENCES

1. *Takeda launches Nesina, Unisia and Vectibix in Japan*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2010, June 16.

2. *Takeda obtains five NDA approvals in Japan*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2010, April 20.

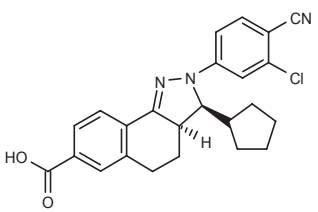
3. *Takeda submits NDA in Japan for Blopress/amlodipine besylate combination*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2009, April 1.

PF-3882845

640715

(3*S*,3a*R*)-2-(3-Chloro-4-cyanophenyl)-3-cyclopentyl-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole-7-carboxylic acid

PF-03882845



C24H22ClN3O2; Mol wt: 419.9030

ACTION – Mineralocorticoid receptor antagonist (IC_{50} = 9 nM in binding assays) that showed selectivity over androgen (IC_{50} > 8910 nM), glucocorticoid (IC_{50} > 10,000 nM), progesterone (IC_{50} = 416 nM) and estrogen receptors (IC_{50} = 10,000 nM). Compound (10 mg/kg p.o.) reduced blood pressure and unrinary albumin excretion and improved glomerulosclerosis in rats, with an oral bioavailability of 86%. Expected to be useful for the treatment of hypertension, heart failure, renal disorders, liver diseases, inflammation, pain, retinopathy, neuropathy, edema and endothelial dysfunction.

SOURCE – Pfizer.

REFERENCES

1. Meyers, M.J. et al. (Pfizer Products Inc.) *Pyrazoline compounds as mineralocorticoid receptor antagonists*. EP 2089367, JP 2010508257, US 2008167294, US 7781428, WO 2008053300.

2. Arhancet, G. *Discovery of clinical candidate PF-3882845, a mineralocorticoid receptor (MR) antagonist for hypertension and nephropathy*. 59th Gordon Res Conf Nat Prod (July 25-30, Tiltol) 2010, Abst.

3. Meyers, M.J. et al. *Discovery of (3S,3aR)-2-(3-Chloro-4-cyanophenyl)-3-cyclopentyl-3,3a,4,5-tetrahydro-2H-benzo[g]indazole-7-carboxylic acid (PF-3882845), an orally efficacious mineralocorticoid receptor (MR) antagonist for hypertension and nephropathy*. J Med Chem 2010, 53(16): 5979.

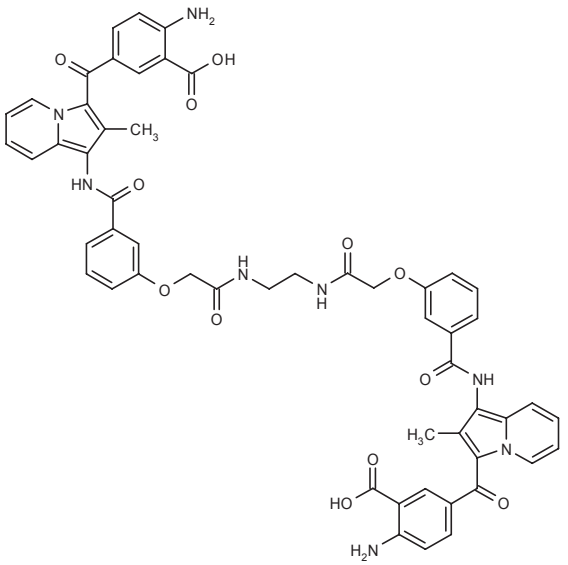
4. *A study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of PF-03882845 in healthy volunteers (NCT00971802)*. ClinicalTrials.gov Web Site 2009, Sept 14.

5. *Multiple dose study in healthy volunteers to assess safety, pharmacokinetics and pharmacodynamics of PF 03882845 (NCT00856258)*. ClinicalTrials.gov Web Site 2009, June 5.

SAR-106881

471293

5,5'-(1,2-Ethylidene)bis(imino)bis(carbonilo)bis(methylene)-bis(oxy)bis(1,3-phenylene)bis(carbonilo)bis(imino)bis(2-methylindolizin-1,3-diyl)bis(carbonilo)bis(2-aminobenzoic acid)



C54H46N8O12; Mol wt: 998.9894

ACTION – Fibroblast growth factor receptor agonist with selectivity for FGFR-4 over FGFR-1β. Compound decreased distal perfusion deficit by 49 and 55%, respectively, in normal mice and *db/db* diabetic mice with hindlimb ischemia when administered at 30 mg/kg/day s.c. for 14 days; it also prevented diabetes-induced mechanical hyperalgesia in Wistar rats with streptozotocin-induced diabetic retinopathy. Potentially as useful as an angiogenesis-inducing agent in the treatment of cardiac ischemia, disorders resulting from arterial obstruction, angina pectoris, atherosclerosis, post-angioplasty restenosis, pain, osteoarthritis, preeclampsia and acute respiratory distress syndrome.

SOURCE – sanofi-aventis.

REFERENCES

1. Bono, F. et al. (sanofi-aventis (FR)) *FGF-receptor agonist dimeric compounds*. EP 2018165, FR 2896247, JP 2009523160, US 2009069368, WO 2007080325.

2. Fons, P. *SAR106881, a fibroblast growth factor receptor agonist aimed at improving peripheral vascularization and wound healing and at reducing neuropathic pain*. Conf Fibroblast Growth Factors Dev Dis (March 14-19, Ventura) 2010, Abst.

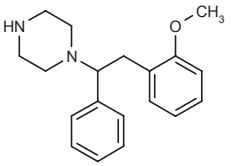
3. Guillo, N. *Making agonists from antagonists: SAR106881, a breakthrough in FGFRs activation and a potential treatment to improve peripheral revascularization and reduce neuropathic pain*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 23.

RENAL-UROLOGIC DRUGS

TREATMENT OF URINARY INCONTINENCE

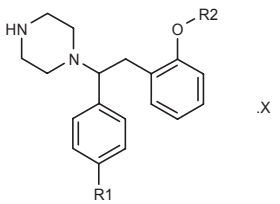
700706[1,3]

(–)-1-[2-(2-Methoxyphenyl)-1-phenylethyl]piperazine



C19H24N2O; Mol wt: 296.4067

ACTION – Dual 5-HT and noradrenaline (NA) reuptake inhibitor that exhibited K_i values of 2 and 12 nM, respectively, against human 5-HT and NA transporters expressed in HEK-293 cells, with selectivity over 5-HT7 and σ receptors (K_i = 840 and 290 nM, respectively). Potentially useful for the treatment of stress urinary incontinence, depression, anxiety, fibromyalgia and painful peripheral neuropathy. Other related compounds are:

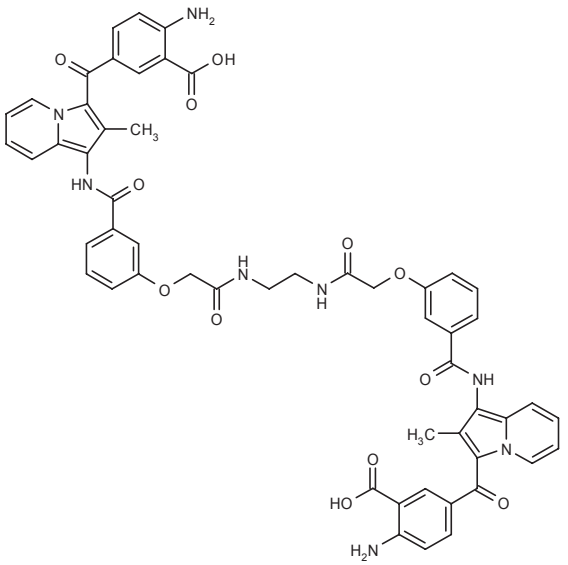


Compound	R1	R2	X	Isomer	Formula
PF-526014 [409990]*[1-4]	H	Et	2HCl	(-), R	$C_{20}H_{28}Cl_2N_2O$
700702[1,3]	F	CF3		(-)	$C_{19}H_{20}F_4N_2O$
700704[1,3]	H	CHF2		(+)	$C_{19}H_{22}F_2N_2O$

SAR-106881

471293

5,5'-(1,2-Ethylidene)bis(imino)bis(carbonilo)bis(methylene)-bis(oxy)bis(1,3-phenylene)bis(carbonilo)bis(imino)bis(2-methylindolizin-1,3-diyl)bis(carbonilo)bis(2-aminobenzoic acid)



C54H46N8O12; Mol wt: 998.9894

ACTION – Fibroblast growth factor receptor agonist with selectivity for FGFR-4 over FGFR-1β. Compound decreased distal perfusion deficit by 49 and 55%, respectively, in normal mice and *db/db* diabetic mice with hindlimb ischemia when administered at 30 mg/kg/day s.c. for 14 days; it also prevented diabetes-induced mechanical hyperalgesia in Wistar rats with streptozotocin-induced diabetic retinopathy. Potentially as useful as an angiogenesis-inducing agent in the treatment of cardiac ischemia, disorders resulting from arterial obstruction, angina pectoris, atherosclerosis, post-angioplasty restenosis, pain, osteoarthritis, preeclampsia and acute respiratory distress syndrome.

SOURCE – sanofi-aventis.

REFERENCES

1. Bono, F. et al. (sanofi-aventis (FR)) *FGF-receptor agonist dimeric compounds*. EP 2018165, FR 2896247, JP 2009523160, US 2009069368, WO 2007080325.

2. Fons, P. *SAR106881, a fibroblast growth factor receptor agonist aimed at improving peripheral vascularization and wound healing and at reducing neuropathic pain*. Conf Fibroblast Growth Factors Dev Dis (March 14-19, Ventura) 2010, Abst.

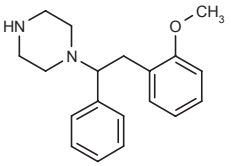
3. Guillo, N. *Making agonists from antagonists: SAR106881, a breakthrough in FGFRs activation and a potential treatment to improve peripheral revascularization and reduce neuropathic pain*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 23.

RENAL-UROLOGIC DRUGS

TREATMENT OF URINARY INCONTINENCE

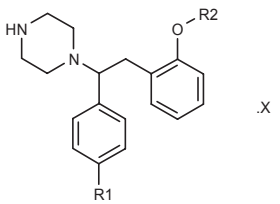
700706[1,3]

(–)-1-[2-(2-Methoxyphenyl)-1-phenylethyl]piperazine



C19H24N2O; Mol wt: 296.4067

ACTION – Dual 5-HT and noradrenaline (NA) reuptake inhibitor that exhibited K_i values of 2 and 12 nM, respectively, against human 5-HT and NA transporters expressed in HEK-293 cells, with selectivity over 5-HT7 and σ receptors (K_i = 840 and 290 nM, respectively). Potentially useful for the treatment of stress urinary incontinence, depression, anxiety, fibromyalgia and painful peripheral neuropathy. Other related compounds are:



Compound	R1	R2	X	Isomer	Formula
PF-526014 [409990]*[1-4]	H	Et	2HCl	(-), R	$C_{20}H_{28}Cl_2N_2O$
700702[1,3]	F	CF3		(-)	$C_{19}H_{20}F_4N_2O$
700704[1,3]	H	CHF2		(+)	$C_{19}H_{22}F_2N_2O$

SOURCE – Pfizer.

REFERENCES

1. Bish, G. et al. (Pfizer Ltd.;Pfizer Inc.) *Piperazine derivatives which exhibit activity as serotonin and noradrenaline re-uptake inhibitors*. EP 1716129, JP 2007517855, US 2007105870, WO 2005068447.

2. Fish, P. *N-(1,2-Diphenylethyl)piperazines: A new class of dual serotonin/noradrenaline reuptake inhibitors*. Drugs Fut 2006, 31(Suppl. A): Abst P45.

3. Fray, M.J. et al. *Second generation N-(1,2-diphenylethyl)piperazines as dual serotonin and noradrenaline reuptake inhibitors: Improving metabolic stability and reducing ion channel activity*. Bioorg Med Chem Lett 2010, 20(12): 3788.

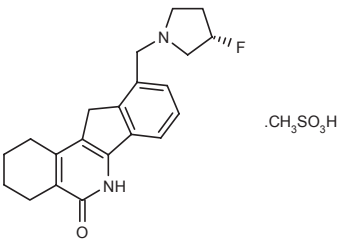
4. Jonathan Fray, M. et al. *Structure-activity relationships of N-substituted piperazine amine reuptake inhibitors*. Bioorg Med Chem Lett 2006, 16(16): 4349.

*Identified compound **409990** Drug Data Rep 2006, 028(09): 0838.

MISCELLANEOUS RENAL-UROLOGIC DRUGS

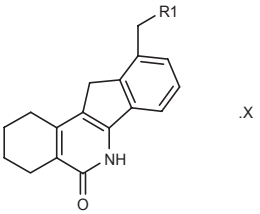
702069

10-[3(*S*)-Fluoropyrrolidin-1-ylmethyl]-2,3,4,5,6,11-hexahydro-1*H*-indeno[1,2-*c*]isoquinolin-5-one methanesulfonate



C22H27FN2O4S; Mol wt: 434.5240

ACTION – Poly(ADP-ribose)polymerase inhibitor that reduced the levels of plasma creatinine, plasma and urine neutrophil gelatinase-associated lipocalin and α-glutathione *S*-transferase in diabetic male Wistar rats with nephropathy at 10 mg/kg i.p. Reported to be useful for the treatment of nephropathy, cardiovascular disorders, cancer, inflammatory diseases, diabetes, neurodegenerative diseases, erectile dysfunction, urinary incontinence and eye disorders. Further applications include the treatement of reperfusion injuries, ischemic conditions, neuropathy, renal failure and complications of prematurity, among others. Related compounds include:



Compound	R1	X	Formula
702074	1-Pip		$C_{22}H_{26}N_2O$
702076	perhydro-1-azepinyl	HCl	$C_{23}H_{29}ClN_2O$
702077	4-Me-1-Pip	mesylate	$C_{24}H_{32}N_2O_4S$

SOURCE – Inotek.

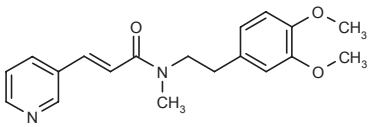
REFERENCES

1. Jagtap, P. et al. (Inotek Pharmaceuticals Corp.) *Substituted tetracyclic 1H-indeno(1,2-b)pyridine-2(5H)-one analogs thereof and uses thereof*. WO 2010077663.

TJN-331*

273146

N-[2-(3,4-Dimethoxyphenyl)ethyl]-*N*-methyl-3-(3-pyridyl)-2(*E*)-propenamide



C19H22N2O3; Mol wt: 326.3896

ACTION – Agent for the treatment of renal diseases such as nephritis, proven to reduce proteinuria, serum cholesterol and blood urea nitrogen in a rat model of nephritis induced by rabbit anti-glomerular basement membrane (GBM) serum following oral administration. Compound inhibited transforming growth factor TGF-β1 production in glomeruli of rats with rabbit anti-GBM serum-induced nephritis at a dose of 2.0 mg/kg/day p.o.

SOURCE – Tsumura.

REFERENCES

1. Hasegawa, Y. et al. (Tsumura & Co.) *Pyridylacrylamide derivatives and nephritis remedies and TGF-beta inhibitors containing the same*. EP 1000935, US 6313153, WO 1999005109.

2. Saegusa, Y. et al. *TJN-331 improves anti-glomerular basement membrane nephritis by Inhibiting the production of intraglomerular transforming growth factor-beta1*. Biol Pharm Bull 2010, 33(8): 1349.

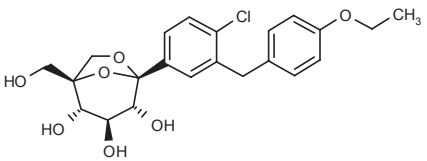
*Identified compound **273146** (see **273144**) Drug Data Rep 1999, 021(04): 0327.

ENDOCRINE DRUGS

TREATMENT OF DIABETES AND RELATED DISEASES

689201*

5(*S*)-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-1(*S*)-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2(*S*),3(*S*),4(*R*)-triol



C22H25ClO7; Mol wt: 436.8830

ACTION – Sodium/glucose cotransporter SGLT2 inhibitor that suppressed human and rat SGLT2 (IC_{50} = 0.88 and 1.15 nM, respectively), with selectivity over human SGLT1 (IC_{50} = 1960 nM). A phase I trial in healthy volunteers showed good pharmacokinetics and a dose-response for urinary glucose excretion, and phase II trials are under way. Potentially useful for the treatment of type 2 diabetes and obesity.

SOURCE – Pfizer.

REFERENCES

1. Mascitti, V. and Collman, B.M. (Pfizer Inc.) *Dioxa-bicyclo[3.2.1]octane-2,3,4-triol derivatives*. US 2010056618, WO 2010023594.

2. Mascitti, V. *Discovery of a new class of SGLT2 inhibitors*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 21.

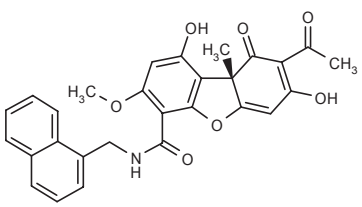
3. Mascitti, V. and Préville, C. *Stereoselective synthesis of a dioxa-bicyclo[3.2.1] octane SGLT2 inhibitor*. Org Lett 2010, 12(13): 2940.

4. Préville, C. and Mascitti, V. *Syntheses of dioxa-bicyclo [3.2.1] octane-2,3,4-triol derivative SGLT2 inhibitors*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst ORGN 930.

*Drug Data Rep 2010, 032(03): 0283.

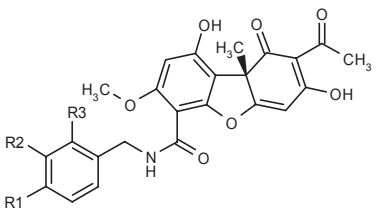
694801

8-Acetyl-1,7-dihydroxy-3-methoxy-9a(*S*)-methyl-*N*-(naphthalen-1-ylmethyl)-9-oxo-9,9a-dihydrodibenzo[*b*,*d*]furan-4-carboxamide



C28H23NO7; Mol wt: 485.4847

ACTION – Selective peroxisome proliferator-activated receptor PPARγ modulator (K_i = 14 nM) that displayed an EC_{50} of 0.18 μM and inhibited agonist-induced transcriptional activity with an IC_{50} of 0.62 μM. Compound dose-dependently (0.01-0.1% in the diet) lowered plasma glucose in hyperglycemic male *db/db* mice, while showing less increase in body weight compared to farglitazar and little or no effect on fluid retention and heart weight. Potentially useful for the treatment of diabetes. Other related compounds are:



Compound	R1	R2	R3	Formula
636743	3-Cl-PhCH2O	-CH=CHCH=CH-		$C_{35}H_{28}ClNO_8$
694802	H	H	Cl	$C_{24}H_{20}ClNO_7$
694805	H	H	H	$C_{24}H_{21}NO_7$

SOURCE – Daiichi Sankyo.

REFERENCES

1. Araki, K. et al. (Daiichi Sankyo Co., Ltd.) *Pharmaceutical compositions containing substituted cercosporamide derivatives*. WO 2008096769.

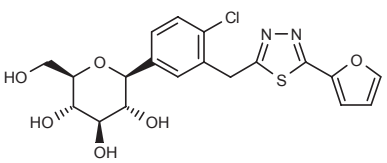
2. Furukawa, S. et al. (Daiichi Sankyo Co., Ltd.) *Medicines containing cercosporamide derivatives*. JP 2008214336.

3. Okuyama, R. et al. (Daiichi Sankyo Co., Ltd.) *Novel cercosporamide derivative*. EP 1914229, JP 2008101016, US 2009036492, WO 2007018193.

4. Furukawa, A. et al. *Discovery of a novel selective PPARgamma modulator from (-)-cercosporamide derivatives*. Bioorg Med Chem Lett 2010, 20(7): 2095.

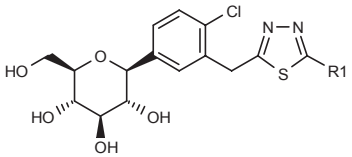
696030

1-[4-Chloro-3-[5-(2-furyl)-1,3,4-thiadiazol-2-ylmethyl]phenyl]-1-deoxy-β-D-glucopyranoside



C19H19ClN2O6S; Mol wt: 438.8820

ACTION – Sodium/glucose cotransporter SGLT2 inhibitor (IC_{50} = 7.03 nM) that strongly increased urinary glucose levels (195 ± 84 mg/200 g body weight) after a single dose of 10 mg/kg p.o. in rats; it also reduced blood glucose levels at a dose of 10 mg/kg p.o. in *db/db* mice. Potentially useful for the treatment of diabetes. Other related compounds are:



Compound	R1	Formula
696033	3-thienyl	$C_{19}H_{19}ClN_2O_5S_2$
696034	2-pyrazinyl	$C_{19}H_{19}ClN_4O_5S$

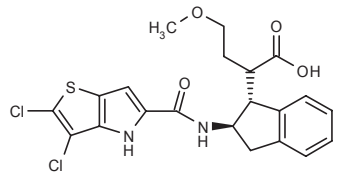
SOURCE – Green Cross.

REFERENCES

1. Lee, J. et al. *Novel C-aryl glucoside SGLT2 inhibitors as potential antidiabetic agents: 1,3,4-Thiadiazolylmethylphenyl glucoside congeners*. Bioorg Med Chem 2010, 18(6): 2178.

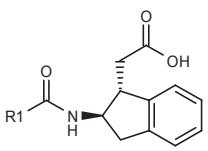
700476[1,3]

2-[(1*R**,2*R**)-(2,3-Dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-ylcarboxamido)-2,3-dihydro-1*H*-inden-1-yl]-4-methoxybutyric acid



C21H20Cl2N2O4S; Mol wt: 467.3650

ACTION – Glycogen phosphorylase type a inhibitor (IC_{50} = 17 nM for recombinant human liver enzyme) that displayed selectivity over cytochrome 450 enzymes (IC_{50} > 10 µM) and the hERG channel (IC_{50} > 30 µM). Oral bioavailability was 118% in rats. A dose of 17 µmol/kg p.o. lowered blood glucose levels by 50% in the glucagon challenge model of diabetes in Zucker rats. Potentially useful for the treatment of type 2 diabetes. Other related compounds are:



Compound	R1	Formula
432400[2,3]	5-F-2-indolyl	$C_{20}H_{17}FN_2O_3$
432407*[1,3]	2,3-(Cl)2-4H-thieno[3,2-b]pyrrol-5-yl	$C_{18}H_{14}Cl_2N_2O_3S$

SOURCE – AstraZeneca.

REFERENCES

1. Birch, A.M. et al. (AstraZeneca AB;AstraZeneca plc) *Chemical compounds*. EP 1848721, JP 2008528667, US 2010137397, WO 2006082401.

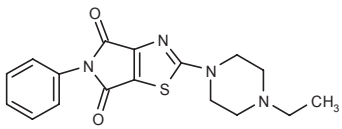
2. Birch, A.M. et al. (AstraZeneca AB;AstraZeneca plc) *Indan-amide derivatives with glycogen phosphorylase inhibitory activity*. EP 1848693, JP 2008528666, US 2009124682, WO 2006082400.

3. Bennett, S.N. et al. *Discovery of a series of indan carboxylic acid glycogen phosphorylase inhibitors*. Bioorg Med Chem Lett 2010, 20(12): 3511.

*Drug Data Rep 2006, 028(09): 0844.

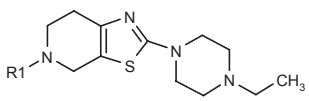
700632

2-(4-Ethylpiperazin-1-yl)-5-phenyl-5,6-dihydro-4*H*-pyrrolo[3,4-*d*]-thiazole-4,6-dione

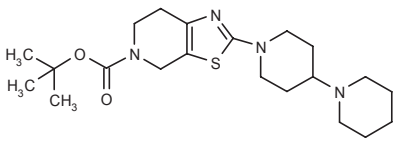


C17H18N4O2S; Mol wt: 342.4150

ACTION – Histamine H3 receptor ligand reported to be useful for the treatment of diabetes, including type 2 diabetes and obesity. Further applications include allergy, allergy-induced airways response, congestion, inflammation, cardiovascular disorders, gastrointestinal disorders and neurological disorders. Related compounds include:



Compound	R1	Formula
700638	cyclopropyl-CO	$C_{16}H_{24}N_4OS$
700641	2,4-(Cl)2-PhNHCO	$C_{19}H_{23}Cl_2N_5OS$
700644	2-thiazolyl	$C_{15}H_{21}N_5S_2$
700648	t-BuOCO	$C_{17}H_{28}N_4O_2S$
700651	2-quinolyl	$C_{21}H_{25}N_5S$
700657	CH2Ph	$C_{19}H_{26}N_4S$



700654: C21H34N4O2S

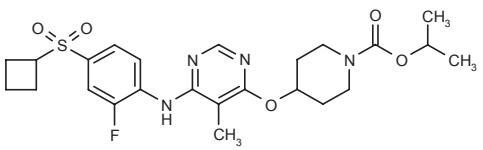
SOURCE – Merck & Co.

REFERENCES

1. Xiao, D. et al. (Schering Corp.) *Piperidine and piperazine derivatives and methods of use thereof*. WO 2010071822.

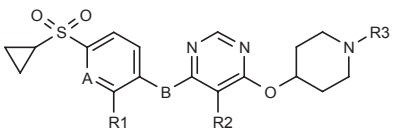
701397

4-[6-[4-(Cyclobutylsulfonyl)-2-fluorophenylamino]-5-methylpyrimidin-4-yloxy]piperidine-1-carboxylic acid isopropyl ester



C24H31FN4O5S; Mol wt: 506.5900

ACTION – Glucose-dependent insulinotropic receptor GPR119 agonist reported to be useful for the treatment of type 2 diabetes, obesity and metabolic syndrome. Related compounds include:



Compound	R1	R2	R3	A	B	Formula
701399	Me	Me	i-PrOCO	N	O	$C_{23}H_{30}N_4O_6S$
701400	F	OMe	i-PrOCO	CH	NH	$C_{23}H_{29}FN_4O_6S$
701401	F	OMe	i-PrOCO	CH	O	$C_{23}H_{28}FN_3O_7S$
701402	F	H	cyclopropyl-SO2	CH	O	$C_{21}H_{24}FN_3O_6S_2$
701404	Cl	H	i-PrOCO	CH	O	$C_{22}H_{26}ClN_3O_6S$
701405	Me	OMe	i-PrOCO	N	NH	$C_{23}H_{31}N_5O_6S$
701406	Me	H	i-PrOCO	N	NH	$C_{22}H_{29}N_5O_5S$

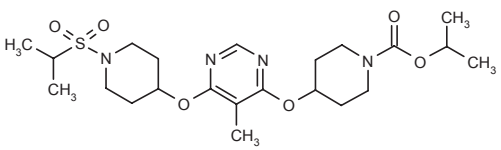
SOURCE – Merck & Co.

REFERENCES

1. Harris, J.M. et al. (Schering Corp.) *Bicyclic heterocycle derivatives and methods of use thereof*. WO 2010075271.

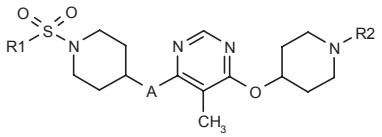
701398

4-[6-[1-(Isopropylsulfonyl)piperidin-4-yloxy]-5-methylpyrimidin-4-yloxy]piperidine-1-carboxylic acid isopropyl ester

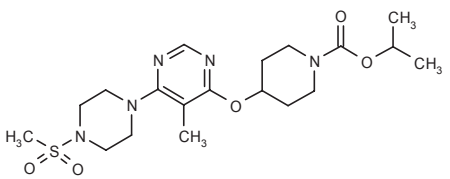


C22H36N4O6S; Mol wt: 484.6090

ACTION – Glucose-dependent insulinotropic receptor GPR119 agonist reported to be useful for the treatment of diabetes, particularly type 2 diabetes, and obesity, as well as metabolic syndrome, diabetic complications and cardiovascular diseases. Related compounds include:



Compound	R1	R2	A	Formula
701415	N(Me)2	i-PrOCO	O	$C_{21}H_{35}N_5O_6S$
701416	allyl	i-PrOCO	O	$C_{22}H_{34}N_4O_6S$
701417	Me	t-BuOCO	O	$C_{21}H_{34}N_4O_6S$
701418	Me	SO2N(Me)2	O	$C_{18}H_{31}N_5O_6S_2$
701419	Me	2,4-(F)2-PhCO	O	$C_{23}H_{28}F_2N_4O_5S$
701420	Me	i-PrOCO	S	$C_{20}H_{32}N_4O_5S_2$



701422: C19H31N5O5S

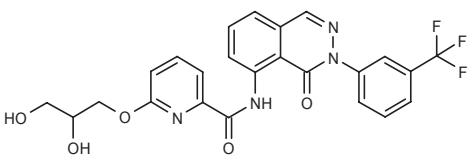
SOURCE – Merck & Co.

REFERENCES

1. Neustadt, B.R. et al. (Schering Corp.) *Pyrimidine derivatives as GPCR modulators for use in the treatment of obesity and diabetes*. WO 2010075269.

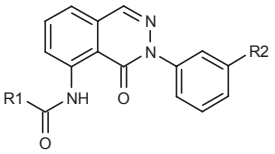
701899

6-(2,3-Dihydroxypropoxy)-*N*-[4-oxo-3-[3-(trifluoromethyl)phenyl]-3,4-dihydrophthalazin-5-yl]pyridine-2-carboxamide



C24H19F3N4O5; Mol wt: 500.4267

ACTION – hSIRT1 activator ($EC_{1.5}$ < 5 μM; fold activation > 150%), potentially useful for the treatment of diabetes and related complications. Related compounds include:



Compound	R1	R2	Formula
701901	4-thiazolyl	CF3	$C_{19}H_{11}F_3N_4O_2S$
701903	6-(4-morpholinyl-CH2)-2-Pyr	CF3	$C_{26}H_{22}F_3N_5O_3$
701906	6-[HOCH2CH(OH)CH2O]-2-Pyr	OCF3	$C_{24}H_{19}F_3N_4O_6$
701907	6-(4-morpholinyl-CH2)-2-Pyr	OCF3	$C_{26}H_{22}F_3N_5O_4$

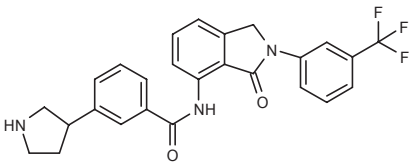
SOURCE – Sirtris Pharmaceuticals.

REFERENCES

1. Vu, C.B. (Sirtris Pharmaceuticals, Inc.) *Phthalazinone and related analogs as sirtuin modulators*. WO 2010077947.

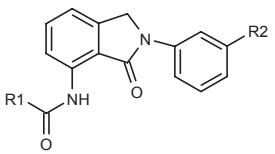
702068

N-[3-Oxo-2-[3-(trifluoromethyl)phenyl]-2,3-dihydro-1*H*-isoindol-4-yl]-3-(3-pyrrolidinyl)benzamide



C26H22F3N3O2; Mol wt: 465.4670

ACTION – hSIRT1 activator ($EC_{1.5}$ < 10 µM; fold activation > 200%), potentially useful for the treatment of diabetes and related complications. Related compounds include:



Compound	R1	R2	Formula
702072	2-pyrazinyl	CF3	$C_{20}H_{13}F_3N_4O_2$
702075	4-THP	CF3	$C_{21}H_{19}F_3N_2O_3$
702078	2-pyrimidinyl	CF3	$C_{20}H_{13}F_3N_4O_2$
702079	4-(1-pyrrolidinyl-CH2)-Ph	CF3	$C_{27}H_{24}F_3N_3O_2$
702082	6-(4-morpholinyl-CH2)-2-Pyr	CF3	$C_{26}H_{23}F_3N_4O_3$
702083	6-(4-morpholinyl-CH2)-2-Pyr	OCF3	$C_{26}H_{23}F_3N_4O_4$

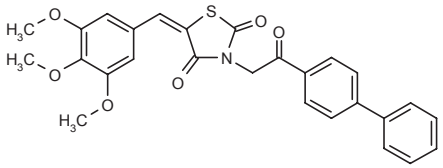
OURCE – Sirtris Pharmaceuticals.

REFERENCES

1. Vu, C.B. et al. (Sirtris Pharmaceuticals, Inc.) *Isoindolinone and related analogs as sirtuin modulators*. WO 2010077686.

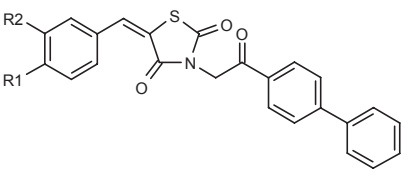
704265

3-[2-(4-Biphenylyl)-2-oxoethyl]-5-(3,4,5-trimethoxybenzylidene)-thiazolidine-2,4-dione

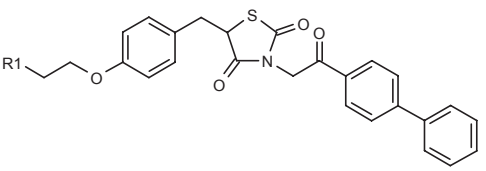


C27H23NO6S; Mol wt: 489.5400

ACTION – Glucose-lowering agent that exhibited hypoglycemic activity with significant reduction of serum glucose and change in body weight in an alloxan-induced diabetic mouse model at 30 mg/kg p.o. Compound proved effective in an oral glucose tolerance test in diabetic mice at 30 mg/kg. In acute oral toxicity tests in diabetic mice it displayed an LD_{50} value > 2000 mg/kg. Reported to be useful for the treatment of type 2 diabetes, dyslipidemia, hypertension, atherosclerosis, eating disorders and cancer, among others. Related compounds include:



Compound	R1	R2	Formula
704266	H	NO2	$C_{24}H_{16}N_2O_5S$
704271	OH	OMe	$C_{25}H_{19}NO_5S$
704273	OH	H	$C_{24}H_{17}NO_4S$



Compound	R1	Formula
704269	2-Pyr-N(Me)	$C_{32}H_{29}N_3O_4S$
704270	5-Et-2-Pyr	$C_{33}H_{30}N_2O_4S$

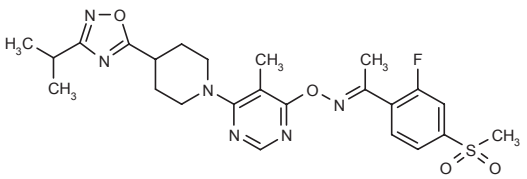
SOURCE – Elder Pharmaceuticals.

REFERENCES

1. Kulkarni, V. et al. (Elder Pharmaceuticals Ltd.) *N-Biphenylacyl thiazolidine-2,4-dione derivatives, their synthesis and uses*. IN 200801299, WO 2010082212.

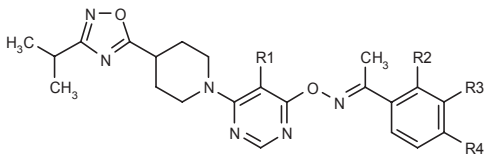
704647

1-[2-Fluoro-4-(methylsulfonyl)phenyl]ethanone *O*-[6-[4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl]-5-methylpyrimidin-4-yl]oxime



C24H29FN6O4S; Mol wt: 516.5880

ACTION – Glucose-dependent insulinotropic receptor GPR119 agonist that activated recombinant human GPR119 receptors by 49.55% at 1 µM in a cAMP assay. When administered orally to C57BL/6 mice at 30 mg/kg it significantly decreased blood glucose levels and it reduced food intake in Sprague-Dawley rats at 25 mg/kg i.p. Expected to be useful for the treatment of diabetes and obesity. Related compounds include:



Compound	R1	R2	R3	R4	Formula
704649	NO2	H	-OCH2O-		$C_{23}H_{25}N_7O_6$
704650	NO2	H	H	OMe	$C_{23}H_{27}N_7O_5$
704651	NO2	H	H	SO2Me	$C_{23}H_{27}N_7O_6S$
704652	NO2	F	H	SO2Me	$C_{23}H_{26}FN_7O_6S$
704654	Me	H	H	CF3	$C_{24}H_{27}F_3N_6O_2$
704655	Me	H	H	OCF3	$C_{24}H_{27}F_3N_6O_3$

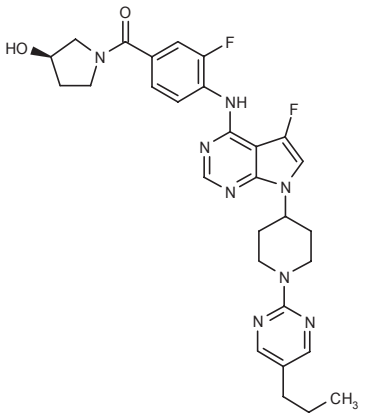
SOURCE – Zydus-Cadila.

REFERENCES

1. Pingali, H. et al. (Zydus-Cadila Group) *Novel oxime derivatives*. WO 2010084512.

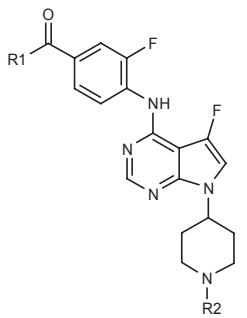
704811

1-[3-Fluoro-4-[5-fluoro-7-[1-(5-propylpyrimidin-2-yl)piperidin-4-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-ylamino]phenyl]-1-[3(*R*)-hydroxypyrrolidin-1-yl]methanone



C29H32F2N8O2; Mol wt: 562.6136

ACTION – Glucose-dependent insulinotropic receptor GPR119 agonist that lowered blood glucose levels in a glucose tolerance test in mice following oral dosing at 3 mg/kg. Expected to be useful for the treatment of diabetes, obesity, dyslipidemia and cardiovascular diseases. Related compounds include:



Compound	R1	R2	Formula
704813	3(R)-OH-1-pyrrolidinyl	5-cyclopropyl-2-pyrimidinyl	$C_{29}H_{30}F_2N_8O_2$
704816	N(Me)CH2CH2OH	5-Cl-2-pyrimidinyl	$C_{25}H_{25}ClF_2N_8O_2$
704817	N(Me)CH2CH2OH	5-i-PrO-2-pyrimidinyl	$C_{28}H_{32}F_2N_8O_3$
704818	1-pyrrolidinyl	i-PrOCO	$C_{26}H_{30}F_2N_6O_3$

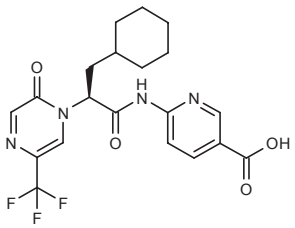
SOURCE – Mitsubishi Tanabe Pharma.

REFERENCES

1. Tsuboi, Y. and Shirai, K. (Mitsubishi Tanabe Pharma Corp.) *Novel pyrrolo[2,3-d]pyrimidine compound*. WO 2010084944.

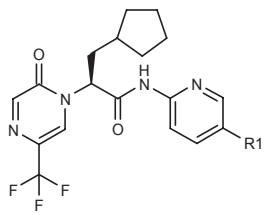
704877

6-[3-Cyclohexyl-2(*S*)-[2-oxo-5-(trifluoromethyl)-1,2-dihydropyrazin-1-yl]propionamido]pyridine-3-carboxylic acid



C20H21F3N4O4; Mol wt: 438.4003

ACTION – Glucokinase activator (EC_{50} = 0.22-0.31 μM) reported to be useful for the treatment of type 2 diabetes, as well as diabetes-related disorders. Other representative compounds are:



Compound	R1	Formula
704879	CO2H	$C_{19}H_{19}F_3N_4O_4$
704882	Me	$C_{19}H_{21}F_3N_4O_2$

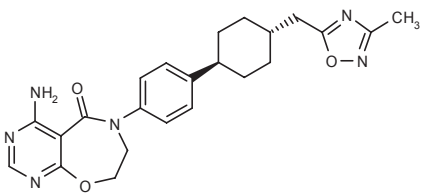
SOURCE – Pfizer.

REFERENCES

1. Benbow, J.W. and Pfefferkorn, J.A. (Pfizer Inc.) *Substituted pyrazinone amides*. US 2010184777, WO 2010084428.

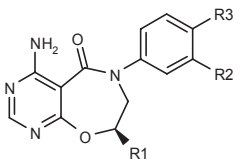
705207

trans-4-Amino-6-[4-[4-(3-methyl-1,2,4-oxadiazol-5-ylmethyl)cyclohexyl]phenyl]-5,6,7,8-tetrahydropyrimido[5,4-*f*][1,4]oxazepin-5-one



C23H26N6O3; Mol wt: 434.4909

ACTION – Diacylglycerol *O*-acyltransferase 1 inhibitor (IC_{50} = 6.05-60 nM) claimed for use in the treatment of type 2 diabetes and diabetes-related disorders. Related compounds are:



Compound	R1	R2	R3	Formula
705197	Me	H	trans-4-(3-Me-1,2,4-oxadiazol-5-yl-CH2)-cyclohexyl	$C_{24}H_{28}N_6O_3$
705198	Me	H	C(Et)2OMe	$C_{20}H_{26}N_4O_3$
705200	Me	H	C(Me)2CF3	$C_{18}H_{19}F_3N_4O_2$
705202	Me	H	i-Bu	$C_{18}H_{22}N_4O_2$
705203	Me	H	3,3-(F)2-cyclobutyl	$C_{18}H_{18}F_2N_4O_2$
705205	Me	-(CH2)3-		$C_{17}H_{18}N_4O_2$
705206	H	H	trans-4-(HOCH2CH2)--cyclohexyl	$C_{21}H_{26}N_4O_3$

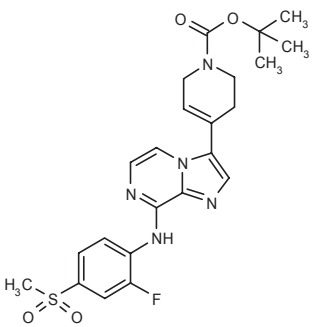
SOURCE – Pfizer.

REFERENCES

1. Aspnes, G.E. et al. (Pfizer Inc.) *4-Amino-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6(5H)-yl)phenyl derivatives, pharmaceutical compositions and uses thereof*. US 2010204119, WO 2010086820.

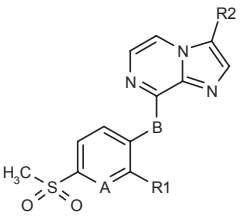
705260

4-[8-[2-Fluoro-4-(methylsulfonyl)phenylamino]imidazo[1,2-*a*]-pyrazin-3-yl]-1,2,3,6-tetrahydropyridine-1-carboxylic acid *tert*-butyl ester

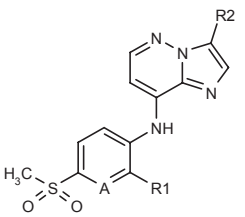


C23H26FN5O4S; Mol wt: 487.5470

ACTION – Glucose-dependent insulinotropic receptor GPR119 agonist ($EC_{50} \leq 10$ μM; efficacy ≤ 50% in HEK-293 cells in cAMP assays), potentially useful for the treatment of diabetes and metabolic diseases. Related compounds include:



Compound	R1	R2	A	B	Formula
705262	F	1-(t-BuOCO)-4-Pip	CH	NH	$C_{23}H_{28}FN_5O_4S$
705278	Me	1-(t-BuOCO)-1,2,3,6-tetrahydro-4-Pyr	N	NH	$C_{23}H_{28}N_6O_4S$
705279	Me	1-(5-Br-2-pyrimidinyl)-1,2,3,6-tetrahydro-4-Pyr	N	NH	$C_{22}H_{21}BrN_8O_2S$
705280	Me	1-(5-cyclopropyl-2-pyrimidinyl)-1,2,3,6-tetrahydro-4-Pyr	N	NH	$C_{25}H_{26}N_8O_2S$
705283	Me	1-(5-Et-2-pyrimidinyl)-1,2,3,6-tetrahydro-4-Pyr	N	O	$C_{24}H_{25}N_7O_3S$



Compound	R1	R2	A	Formula
705282	F	1-(5-Et-2-pyrimidinyl)-1,2,3,6-tetrahydro-4-Pyr	CH	$C_{24}H_{24}FN_7O_2S$
705284	Me	1-(5-Et-2-pyrimidinyl)-4-Pip	N	$C_{24}H_{28}N_8O_2S$

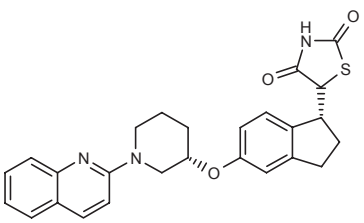
SOURCE – Kalypsys.

REFERENCES

1. Kahraman, M. et al. (Kalypsys, Inc.) *Heterocyclic modulators of GPR119 for treatment of disease.* WO 2010088518.

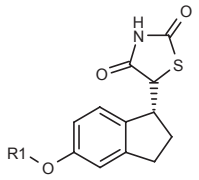
705485

5-[5-[1-(2-Quinolinyl)piperidin-3(*S*)-yloxy]-2,3-dihydro-1*H*-inden-1(*R*)-yl]thiazolidine-2,4-dione



C26H25N3O3S; Mol wt: 459.5600

ACTION – Free fatty acid FFA1 receptor agonist reported to be useful for the treatment of type 2 diabetes and related disorders. Other representative compounds are:



Compound	R1	Formula
705486	1-[3,5-(F)2-Ph]-3(S)-Pip	$C_{23}H_{22}F_2N_2O_3S$
705487	1-(5-F-2-Pyr)-4-Pip	$C_{22}H_{22}FN_3O_3S$
705488	1-(MeSO2)-1,2,3,4-tetrahydro-4-quinolyl	$C_{22}H_{22}N_2O_5S_2$
705489	1-(CF3CH2)-8-F-1,2,3,4-tetrahydro-4-quinolyl	$C_{23}H_{20}F_4N_2O_3S$
705490	2-(CF3CH2)-1-oxo-1,2,3,4-tetrahydro-4-isoquinolyl	$C_{23}H_{19}F_3N_2O_4S$
705493	2-i-Bu-1-oxo-1,2,3,4-tetrahydro-4-isoquinolyl	$C_{25}H_{26}N_2O_4S$
705495	2-(MeSO2)-1,2,3,4-tetrahydro-4-isoquinolyl	$C_{22}H_{22}N_2O_5S_2$

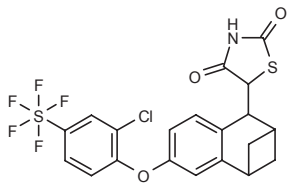
SOURCE – Merck & Co.

REFERENCES

1. Josien, H.B. et al. (Schering Corp.) *Bridged and fused heterocyclic antidiabetic compounds.* WO 2010085525.

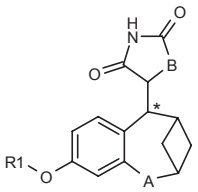
705526

5-[7-[2-Chloro-4-(pentafluorosulfanyl)phenoxy]-1,2,3,4-tetrahydro-1,3-methanonaphthalen-4-yl]thiazolidine-2,4-dione

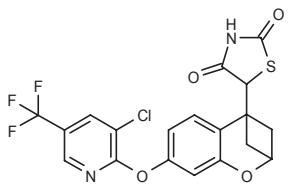


C20H15ClF5NO3S2; Mol wt: 511.9130

ACTION – Free fatty acid FFA1 receptor agonist reported to be useful for the treatment of type 2 diabetes and related disorders. Related compounds include:



Compound	R1	A	B	*Isomer	Formula
705527	2-Cl-4-CF3-Ph	bond	S	R	$C_{21}H_{15}ClF_3NO_3S$
705528	2-Cl-4-CN-Ph	bond	S	R	$C_{21}H_{15}ClN_2O_3S$
705530	4-CF3-1-phthalazinyl	bond	S	R	$C_{23}H_{16}F_3N_3O_3S$
705531	4-CN-1-phthalazinyl	bond	S	R	$C_{23}H_{16}N_4O_3S$
705532	2-Cl-4-CF3-Ph	bond	O	R	$C_{21}H_{15}ClF_3NO_4$
705533	4-CN-1-Naph	O	S		$C_{25}H_{18}N_2O_4S$



705534: C19H12ClF3N2O4S

SOURCE – Merck & Co.

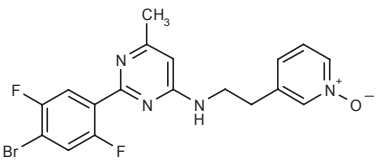
REFERENCES

1. Josien, H.B. et al. (Schering Corp.) *Bridged and fused antidiabetic compounds*. WO 2010085528.

AS-1669058

706575

2-(4-Bromo-2,5-difluorophenyl)-6-methyl-*N*-[2-(1-oxidopyridin-3-yl)ethyl]pyrimidin-4-amine



C18H15BrF2N4O; Mol wt: 421.2390

ACTION- Glucose-dependent insulinotropic receptor GPR119 agonist (EC_{50} = 0.11 μM) with reduced cytochrome CYP1A2- and hERG-inhibitory activity (47% at 100 μM), that increased glucose-dependent insulin secretion in rat islets and reduced plasma glucose and increased pancreatic insulin levels in diabetic *db/db* mice at 3 mg/kg p.o. b.i.d. for 1 week. Oral bioavailability was 57% in mice and 16% in monkeys. Potentially useful for the treatment of type 2 diabetes.

SOURCE – Astellas Pharma.

REFERENCES

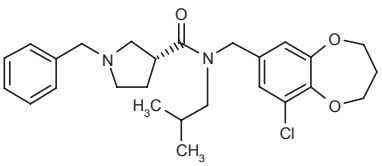
1. Yonetoku, Y. et al. (Astellas Pharma Inc.) *Insulin secretion accelerator and novel pyrimidine derivative*. WO 2003026661.

2. Yonetoku, Y. et al. *Discovery of aminopyrimidine derivatives as novel GPR119 receptor agonists*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 392.

3Cl-R-PLP

701914

1-Benzyl-*N*-(9-chloro-3,4-dihydro-2*H*-1,5-benzodioxepin-7-ylmethyl)-*N*-isobutylpyrrolidine-3(*R*)-carboxamide



C26H33ClN2O3; Mol wt: 457.0050

ACTION – Prokineticin receptor antagonist with K_i values of 2.66 and 23.4 nM, respectively, for PKR1 and PKR2 receptors in Ca^{2+} mobilization assays in CHO cells. In an oral glucose tolerance test in mice compound significantly and dose-dependently improved glucose clearance at 1-40 mg/kg by gavage. It effectively decreased glucose levels in diet-induced diabetic mice (0.1 and 0.01 mg/mL) and *db/db* mice under both fed and fasting conditions (0.1 mg/mL in drinking water). Reported to be useful for the treatment of type 2 diabetes, as well as for the treatment of sleep disorders, ischemic stroke, gastrointestinal motility disorders, pain, anxiety and mood disorders.

SOURCE – University of California, Oakland, Oakland, CA (US).

REFERENCES

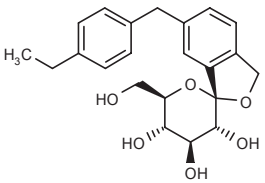
1. Zhou, Q.-Y. et al. (University of California, Oakland) *Prokineticin receptor antagonists and uses thereof*. WO 2010077976.

CSG-452*[1-3]

432224

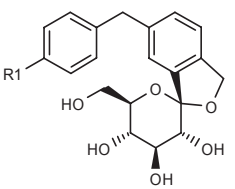
(1*S*,3'*R*,4'*S*,5'*S*,6'*R*)-6-(4-Ethylbenzyl)-6'-(hydroxymethyl)-3',4',5',6'-tetrahydro-3*H*-spiro[2-benzofuran-1,2'-pyran]-3',4',5'-triol

RG-7201
R-7201



C22H26O6; Mol wt: 386.4382

ACTION – Selective sodium/glucose cotransporter SGLT2 inhibitor (IC_{50} = 2.9 and 8444 nM, respectively, for human SGLT2 and SGLT1 in CHO cells) that exhibited good oral bioavailability of 75 and 85%, respectively, in mice and monkeys. Compound lowered blood glucose levels in *db/db* mice at doses of 1-10 mg/kg p.o. and increased urinary glucose excretion (MED = 3 mg/kg p.o.). Potentially useful for the treatment of type 2 diabetes. Other related compounds are:



Compound	R1	Formula
432225**[1,3]	i-Pr	$C_{23}H_{28}O_6$
706163[1,3]	cyclopropyl	$C_{23}H_{26}O_6$

SOURCES – Chugai Pharmaceutical; Roche.

REFERENCES

1. Kobayashi, T. et al. (Chugai Pharmaceutical Co. Ltd.) *Spiroketal derivative and use thereof as diabetic medicine*. EP 1852439, US 2009030006, US 7767651, WO 2006080421.

2. Murakata, M. et al. (Chugai Pharmaceutical Co. Ltd.) *Crystal of spiroketal derivative, and process for production thereof*. WO 2009154276.

3. Sato, T. et al. *Discovery of O-spiroketal C-arylglucosides as novel and selective sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor for the treatment of type diabetes*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 202.

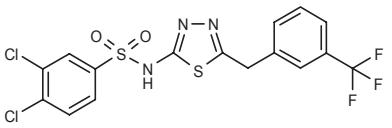
*Identified compound **432224** (see **432223**) Drug Data Rep 2006, 028(09): 0844.

Identified compound **432225 (see **432223**) Drug Data Rep 2006, 028(09): 0844.

L-201

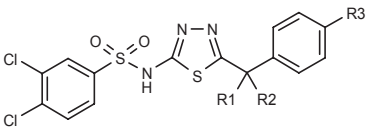
701119

3,4-Dichloro-*N*-[5-[3-(trifluoromethyl)benzyl]-1,3,4-thiadiazol-2-yl]-benzenesulfonamide

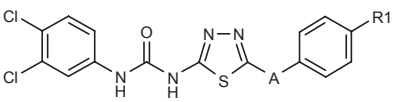


C16H10Cl2F3N3O2S2; Mol wt: 468.3010

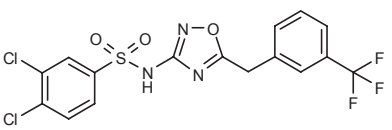
ACTION – AMP-activated protein kinase (AMPK) activator that displayed a significant decrease in fed blood glucose (on day 12 and 20) compared to control in diabetic *ob/ob* mice treated with 30 mg/kg p.o. b.i.d. for 20 days, whereas it showed no significant increase in plasma insulin levels in C57BL/6JBomTac mice compared to control. Reported to be useful for the treatment of hyperinsulinemia, type 2 diabetes, cancer, fibrosis, neurodegenerative diseases, sexual dysfunction, heart failure, inflammation and osteoporosis. Further applications include skin diseases, lung diseases, obesity, age-related macular degeneration and cardioprotection. Related compounds include:



Compound	R1	R2	R3	Formula
701121	-CH2CH2-		Cl	$C_{17}H_{12}Cl_3N_3O_2S_2$
701122	H	H	CF3	$C_{16}H_{10}Cl_2F_3N_3O_2S_2$



Compound	R1	A	Formula
701123	F	-SCH2-	$C_{16}H_{11}Cl_2FN_4OS_2$
701124	H	-CH2S-	$C_{16}H_{12}Cl_2N_4OS_2$



701120: C16H10Cl2F3N3O3S

SOURCE – Betagenon.

REFERENCES

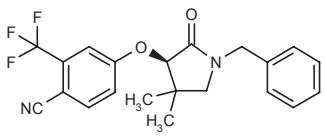
1. Westman, J. (Betagenon AB) *Compounds useful as medicaments*. WO 2010073011.

DERMATOLOGIC DRUGS

ACNE THERAPY

658872

4-[1-Benzyl-4,4-dimethyl-2-oxopyrrolidin-3(*R*)-yloxy]-2-(trifluoromethyl)benzonitrile



C21H19F3N2O2; Mol wt: 388.3830

ACTION – Nonsteroidal androgen receptor (AR) antagonist (IC_{50} = 100 nM for the human receptor in a binding assay), with selectivity over the progesterone receptor (IC_{50} = 4400 nM in a binding assay) and glucocorticoid, estrogen and thyroid hormone receptors (IC_{50} > 10 µM). Compound reduced wax and cholesterol esters in golden Syrian hamsters. Potentially useful for the treatment of acne, alopecia and excess sebum secretion.

SOURCE – Pfizer.

REFERENCES

1. Barrett, S.D. et al. (Pfizer Inc.) *Androgen modulators*. EP 1888524, JP 2008540397, US 2006252796, WO 2006117677.

2. Barrett, S.D. et al. (Pfizer Inc.) *Androgen modulators*. US 2007072936, US 7799823.

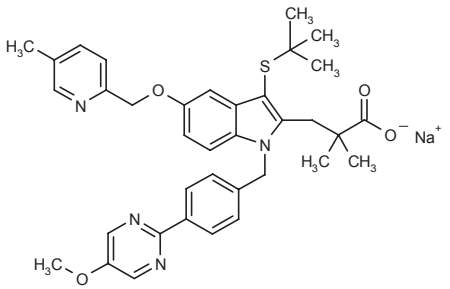
3. Huang, T.Y. et al. *Rational design of a topical androgen receptor antagonist for the suppression of sebum production with properties suitable for follicular delivery*. J Med Chem 2010, 53(11): 4422.

MISCELLANEOUS DERMATOLOGIC DRUGS

AM-643

702234

3-[3-(*tert*-Butylsulfanyl)-1-[4-(5-methoxypyrimidin-2-yl)benzyl]-5-(5-methylpyridin-2-ylmethoxy)-1*H*-indol-2-yl]-2,2-dimethylpropionic acid sodium salt



C36H39N4NaO4S; Mol wt: 646.7740

ACTION – 5-Lipoxygenase-activating protein (FLAP) inhibitor (IC_{50} = 2 nM in binding assays) that inhibited leukotriene LTB_4 synthesis in calcium ionophore-stimulated human leukocytes (IC_{50} = 0.6 nM) and whole blood (IC_{50} = 81, 4 and 11 nM, respectively, in human, mouse and rat blood), with minimal inhibition of cytochrome P450 enzymes and no inhibition of COX-1 enzyme (> 100 µM). Compound 30 mg/kg p.o. and 0.01-0.1% topically significantly decreased arachidonic acid-induced ear swelling, cysteinyl leukotrienes and LTB_4 concentrations in mice. Potentially useful for the treatment of skin disorders, asthma, allergy and inflammation.

SOURCE – Amira Pharmaceuticals.

REFERENCES

1. Hutchinson, J.H. et al. (Amira Pharmaceuticals, Inc.) *5-Lipoxygenase-activating protein (FLAP) inhibitors*. CA 2628467, EP 1943266, JP 2009514959, WO 2007056228.

2. Hutchinson, J.H. et al. (Amira Pharmaceuticals, Inc.) *Topical formulations of FLAP inhibitors for administration to an eye*. WO 2010075315.

3. Hutchinson, J.H. et al. (Amira Pharmaceuticals, Inc.) *Topical formulations of FLAP inhibitors for the treatment of dermatological conditions*. WO 2010075314.

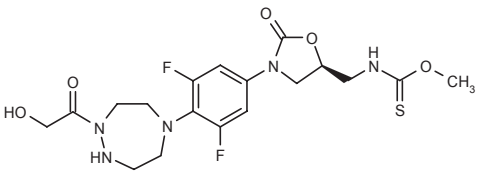
4. Stock, N. et al. *5-Lipoxygenase-activating protein inhibitors. Part 3: 3-{3-tert-Butylsulfanyl-1-[4-(5-methoxy-pyrimidin-2-yl)-benzyl]-5-(5-methyl-pyridin-2-ylmethoxy)-1H-indol-2-yl]-2,2-dimethyl-propionic acid (AM643)-A potent FLAP inhibitor suitable for topical administration*. Bioorg Med Chem Lett 2010, 20(15): 4598.

ANTIINFECTIVE THERAPY

ANTIBIOTICS AND ANTIBACTERIAL DRUGS

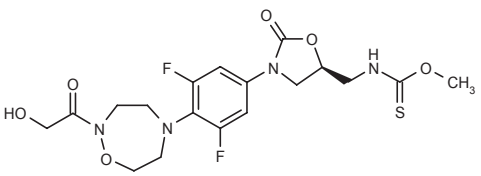
702467

N-[3-[3,5-Difluoro-4-[1-(2-hydroxyacetyl)perhydro-1,2,5-triazepin-5-yl]phenyl]-2-oxooxazolidin-5(*S*)-ylmethyl]thiocarbamic acid *O*-methyl ester



C18H23F2N5O5S; Mol wt: 459.4680

ACTION – Oxazolidinone with MIC values of 0.25, 2, 0.25 and 0.125 µg/mL, respectively, against methicillin- and linezolid-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecium* and *Streptococcus pneumoniae*. It demonstrated efficacy in mice systemically infected with *S. aureus* (ED_{50} = 0.77 mg/kg i.v.). Another related compound is:



702469: C18H22F2N4O6S

SOURCES – Research Foundation Itsuu Laboratory, Tokyo (JP); Shionogi.

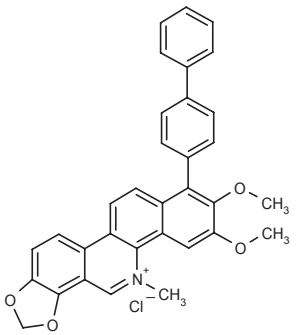
REFERENCES

1. Suzuki, H. et al. (Research Foundation Itsuu Laboratory;Shionogi & Co. Ltd.) *Oxazolidinone derivative having 7-membered hetero ring*. EP 2208729, EP 2233484, WO 2009044777.

2. Suzuki, H. et al. *Synthesis and application of [1,2,5]triazepane and [1,2,5]oxadiazepane as versatile structural units for drug discovery*. Chem Pharm Bull 2010, 58(7): 1001.

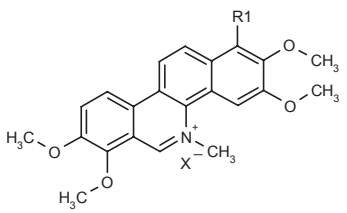
704392

8-(4-Biphenylyl)-9,10-dimethoxy-12-methylbenzo[*c*][1,3]dioxolo[4,5-*i*]phenanthridin-12-ium chloride

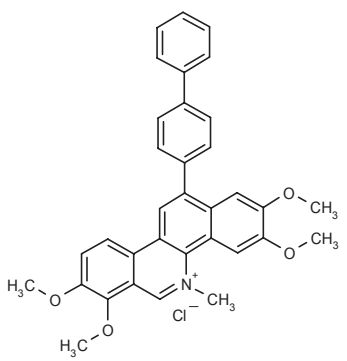


C33H26ClNO4; Mol wt: 536.0170

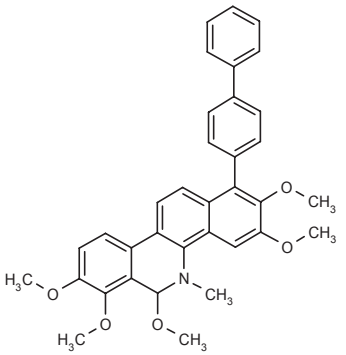
ACTION – GTPase inhibitor that showed activity against *Staphylococcus aureus*, methicillin-resistant *S. aureus*, *Mycobacterium tuberculosis*, *Enterococcus faecalis* and *Bacillus subtilis* with MIC values of 2, 8, 4, 16 and 2 µg/mL, respectively. Related compounds include:



Compound	R1	X⁻	Formula
704394	4-Ph-Ph	Cl	$C_{34}H_{30}ClNO_4$
704396	1-cyclohexenyl	Cl	$C_{28}H_{30}ClNO_4$
704397	Ph	Cl	$C_{28}H_{26}ClNO_4$
704398	3,4,5-(MeO)3-Ph	CO2CF3	$C_{33}H_{32}F_3NO_9$
704399	3-furyl	CO2CF3	$C_{28}H_{24}F_3NO_7$



704400: C34H30ClNO4



704401: C35H33NO5

SOURCES – University of Medicine and Dentistry of New Jersey, Newark, NJ (US); State University of New Jersey (Rutgers), Piscataway, NJ (US).

REFERENCES

1. Pilch, D.S. et al. (University of Medicine and Dentistry of New Jersey;State University of New Jersey (Rutgers)) *Benzo[c]phenanthridines as antimicrobial agents*. WO 2010083436.

706507

Glycyl-L-lysyl-L-tryptophyl-L-methionyl-L-lysyl-L-leucyl-L-leucyl-L-lysyl-L-histidyl-L-isoleucyl-L-leucyl-L-lysinamide

C72H124N20O12S; Mol wt: 1493.9470

ACTION – Peptide with antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* (MIC = 0.8, 4.5, 2.5 and 10.7 μM, respectively). Reported to be useful for the treatment of bacterial, viral, parasitic and fungal infections as well as cancer. Related compounds include:

Glycyl-L-methionyl-L-tryptophyl-L-seryl-L-lysyl-L-isoleucyl-L-leucyl-glycyl-L-histidyl-L-leucyl-L-isoleucyl-L-argininamide

706509: C65H108N20O13S

Glycyl-L-lysyl-L-tryptophyl-L-methionyl-L-seryl-L-leucyl-L-leucyl-L-lysyl-L-histidyl-L-isoleucyl-L-leucyl-L-lysinamide

706510: C69H117N19O13S

Glycyl-L-methionyl-L-tryptophyl-L-seryl-L-lysyl-L-isoleucyl-L-leucylglycyl-L-histidyl-L-leucyl-L-isoleucyl-L-lysinamide

706511: C65H108N18O13S

Glycyl-L-methionyl-L-tryptophyl-L-lysyl-L-lysyl-L-isoleucyl-L-leucyl-glycyl-L-histidyl-L-leucyl-L-isoleucyl-L-argininamide

706513: C68H115N21O12S

Glycyl-L-lysyl-L-tryptophyl-L-lysyl-L-lysyl-L-isoleucyl-L-leucyl-glycyl-L-lysyl-L-leucyl-L-isoleucyl-L-argininamide

706514: C69H123N21O12

Glycyl-L-lysyl-L-tryptophyl-L-methionyl-L-seryl-L-leucyl-L-leucyl-L-lysyl-L-lysyl-L-isoleucyl-L-leucyl-L-lysinamide

706516: C69H122N18O13S

SOURCE – Ústav Organické Chemie a Biochemie, Prague (CZ).

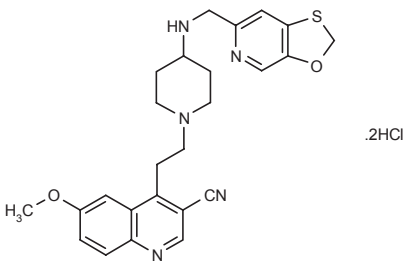
REFERENCES

1. Monincova, L. et al. (Ústav Organické Chemie a Biochemie AV CR, vvi) *Novel antimicrobial peptides*. WO 2010091651.

GSK-299423

705655

6-Methoxy-4-[2-[4-(1,3-oxathiolo[5,4-*c*]pyridin-6-ylmethylamino)-piperidin-1-yl]ethyl]quinoline-3-carbonitrile dihydrochloride



C25H29Cl2N5O2S; Mol wt: 534.5010

ACTION – DNA topoisomerase 2-α inhibitor (IC_{50}= 14 and 100 nM, respectively, against *Staphylococcus aureus* and *Escherichia coli* enzymes) that displayed antibacterial activity against *S. aureus*, methicillin- and quinolone-resistant *S. aureus*, *Streptococcus pneumoniae*, quinolone-resistant *S. pneumoniae*, *Streptococcus pyogenes*, *Enterococcus faecalis*, *Enterococcus faecium*, *Haemophilus influenzae*, quinolone-resistant *H. influenzae*, *Moraxella catarrhalis*, *E. coli*, *Enterobacter cloacae*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* (MIC ≤ 0.016, ≤ 0.016, ≤ 0.016, 0.063, ≤ 0.016, 0.125, 0.19, 0.25, 0.25, ≤ 0.016, 0.063, 2, 4, 0.5, 8 and 1 μg/mL, respectively).

SOURCE – GlaxoSmithKline.

REFERENCES

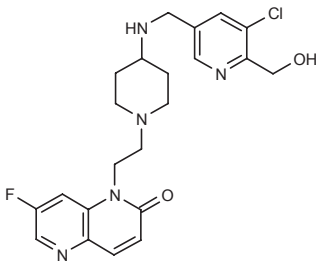
1. Hennessy, A.J. et al. (GlaxoSmithKline plc) *Antibacterial agents*. EP 1605938, JP 2006521401, WO 2004087145.

2. Bax, B.D. et al. *Type IIA topoisomerase inhibition by a new class of antibacterial agents*. Nature 2010, 466(7309): 935.

ANTIMYCOBACTERIAL AGENTS

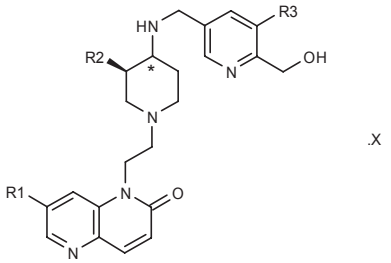
704248

1-[2-[4-[5-Chloro-6-(hydroxymethyl)pyridin-3-ylmethylamino]piperidin-1-yl]ethyl]-7-fluoro-1,5-naphthyridin-2(1*H*)-one



C22H25ClFN5O2; Mol wt: 445.9180

ACTION – Compound with activity against M*ycobacterium tuberculosis* H37Rv (MIC < 0.3 µg/mL). Other representative compounds are:



Compound	R1	R2	R3	*Isomer	X	Formula
704239	F	H	Br			$C_{22}H_{25}BrFN_5O_2$
704241	OMe	H	Cl			$C_{23}H_{28}ClN_5O_3$
704242	F	OH	Cl	S	HCl	$C_{22}H_{26}Cl_2FN_5O_3$
704244	F	OH	Cl	S		$C_{22}H_{25}ClFN_5O_3$
704245	F	H	Cl		HCl	$C_{22}H_{26}Cl_2FN_5O_2$

SOURCE – GlaxoSmithKline.

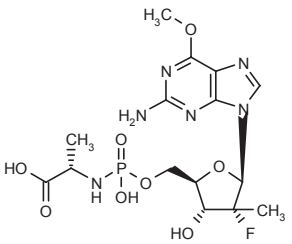
REFERENCES

1. Alemparte-Gallardo, C. et al. (GlaxoSmithKline plc) *Naphthyridin-2(1H)-one compounds useful as antibacterials*. WO 2010081874.

ANTIVIRAL DRUGS

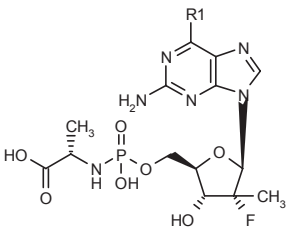
700946

2-Amino-6-methoxy-9-[2-deoxy-2-fluoro-2-methyl-5-*O*-[(L-alanino)(hydroxy)phosphoryl]-β-D-ribofuranosyl]-9*H*-purine

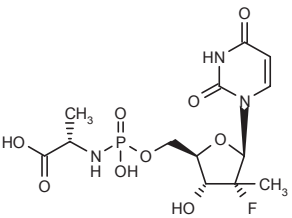


C15H22FN6O8P; Mol wt: 464.3427

ACTION – Nucleoside derivative acting as an RNA-directed RNA polymerase NS5B inhibitor, reported to be useful for the treatment of viral infections, in particular hepatitis C virus, as well as West Nile, yellow fever, dengue, Japanese encephalitis and rhinoviruses and bovine viral diarrhea. Related compounds include:



Compound	R1	Formula
700950	OEt	$C_{16}H_{24}FN_6O_8P$
700953	1-azetidinyl	$C_{17}H_{25}FN_7O_7P$
700954	OH	$C_{14}H_{20}FN_6O_8P$



700956: C13H19FN3O9P

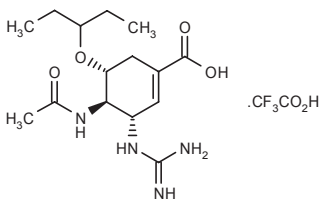
SOURCE – Pharmasset.

REFERENCES

1. Bao, D. et al. (Pharmasset, Inc.) *Nucleoside analogs*. WO 2010075517.

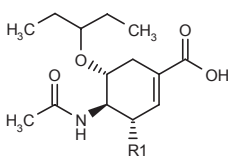
701858

4(*R*)-Acetamido-3(*S*)-guanidino-5(*R*)-(pentan-3-yloxy)-1-cyclohexene-1-carboxylic acid trifluoroacetate



C17H27F3N4O6; Mol wt: 440.4147

ACTION – Neuraminidase inhibitor that inhibited virus-like particles with influenza virus N1 activity with a K_i value of 4.8 nM. Related compounds include:



Compound	R1	Formula
701859	NH2	$C_{14}H_{24}N_2O_4$
701860	4-[CH(OH)Et]-1,2,3-triazol-1-yl	$C_{19}H_{30}N_4O_5$
701862	4-[(CH2)3OH]-1,2,3-triazol-1-yl	$C_{19}H_{30}N_4O_5$
701863	4-[C(Me)2OH]-1,2,3-triazol-1-yl	$C_{19}H_{30}N_4O_5$

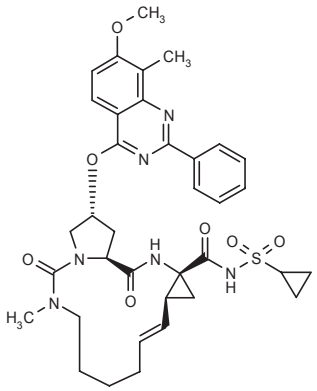
SOURCE – Simon Fraser University, Burnaby, BC (CA).

REFERENCES

1. Pinto, B.M. and Mohan, S. (Simon Fraser University) *Compounds and methods for treatment of influenza*. WO 2010075636.

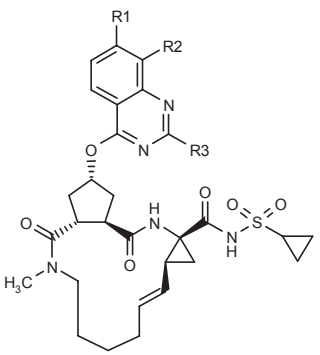
702376

N-[(2*R*,12a*S*,13a*R*,15a*S*)-2-(7-Methoxy-8-methyl-2-phenylquinazolin-4-yloxy)-6-methyl-5,15-dioxo-2,3,5,6,7,8,9,10,12a,13,13a,14,15,15a-tetradecahydro-1*H*-cyclopropa[*g*]pyrrolo[1,2-*c*][1,3,6]triazacyclotetradecin-13a-ylcarbonyl]cyclopropanesulfonamide

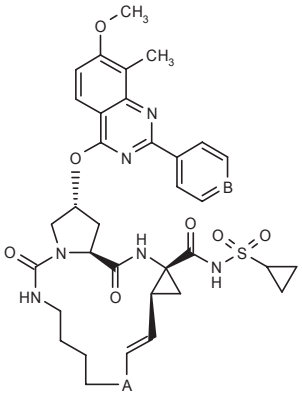


C36H42N6O7S; Mol wt: 702.8200

ACTION – Hepatitis C virus (HCV) NS3/4A protease inhibitor (K_i = 0.2 nM) that inhibited HCV RNA replication with an EC_{50} of 11 nM in a cell-based luciferase reporter assay. Oral bioavailability was 73% in rats. Other related compounds are:



Compound	R1	R2	R3	Formula
445030	OMe	H	Ph	$C_{36}H_{41}N_5O_7S$
445031	H	H	4-i-Pr-2-thiazolyl	$C_{35}H_{42}N_6O_6S_2$
445035	OMe	Me	4-MeO-Ph	$C_{38}H_{45}N_5O_8S$
445036	OMe	Me	3-F-Ph	$C_{37}H_{42}FN_5O_7S$
702375	OMe	Me	Ph	$C_{37}H_{43}N_5O_7S$



Compound	A	B	Formula
445033	bond	C(F)	$C_{36}H_{41}FN_6O_7S$
445037	bond	N	$C_{35}H_{41}N_7O_7S$
702377	CH2	C(F)	$C_{36}H_{41}FN_6O_7S$

SOURCES – Medivir; Tibotec.

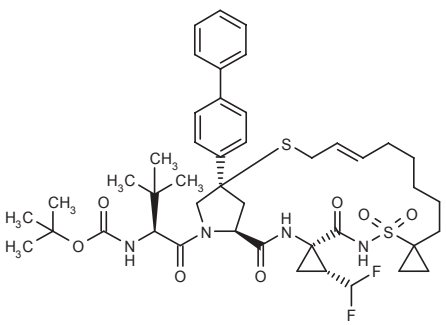
REFERENCES

1. Raboisson, P.J.-M.B. et al. (Tibotec Pharmaceuticals Ltd.;Medivir AB) *Macrocyclic inhibitors of hepatitis C virus*. EP 1912981, JP 2009502890, US 2009118312, US 7659245, WO 2007014927.

2. Nilsson, M. et al. *Synthesis and SAR of potent inhibitors of the Hepatitis C virus NS3/4A protease: Exploration of P2 quinazoline substituents*. Bioorg Med Chem Lett 2010, 20(14): 4004.

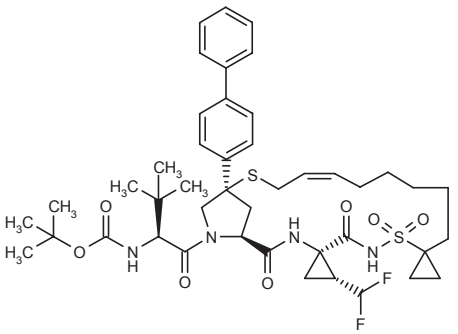
702474

N-[1-[(1*R*,1'*S*,2*R*,14'*E*,18'*R*)-18'-(4-Biphenylyl)-2-(difluoromethyl)-2',5',7',7'-tetraoxo-7',17'-dithia-3',6',20'-triazadispiro[cyclopropane-1,4'-bicyclo[16.2.1]henicosane-8',1''-cyclopropane]-14'-en-20'-yl]-3,3-dimethyl-1-oxobutan-2(*S*)-yl]carbamic acid *tert*-butyl ester



C44H58F2N4O7S2; Mol wt: 857.0810

ACTION – Hepatitis C virus (HCV) NS3/NS4A protease inhibitor (IC_{50} = 2 nM) that suppressed HCV genotype 1a and 1b replication (EC_{50} = 49 and 21 nM, respectively) in Huh-7 cells in HCV replicon luciferase reporter assays. Another representative compound is:



702477: C44H58F2N4O7S2

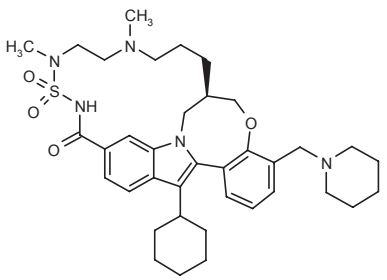
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Wang, A.X. and Scola, P.M. (Bristol-Myers Squibb Co.) *Hepatitis C virus inhibitors*. US 2010150866, WO 2010077783.

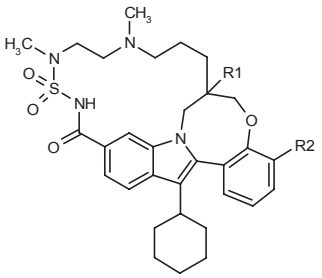
704276

14-Cyclohexyl-18,21-dimethyl-4-(piperidin-1-ylmethyl)-7,8-dihydro-6*H*-7(*R*),11-(propanoiminoethanoiminothioiminomethano)indolo-[1,2-*e*][1,5]benzoxazocin-15-one 17,17-dioxide

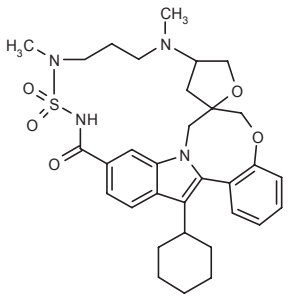


C37H51N5O4S; Mol wt: 661.8970

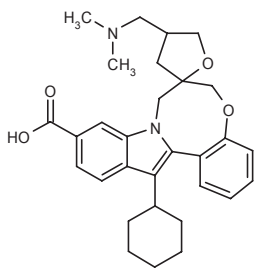
ACTION – RNA-directed RNA polymerase NS5B inhibitor that suppressed hepatitis C virus replication in Huh-7 cells with with an EC_{50} < 25 nM. Other representative compounds are:



Compound	R1	R2	Isomer	Formula
704280	H	3,3-(F)2-1--pyrrolidinyl-CH2	R	$C_{36}H_{47}F_2N_5O_4S$
704281	H	1-pyrrolidinyl-(CH2)3	R	$C_{38}H_{53}N_5O_4S$
704283	H	4-morpholinyl-CH2	R	$C_{36}H_{49}N_5O_5S$
704284	OH	Me		$C_{32}H_{42}N_4O_5S$
704296	F	H		$C_{31}H_{39}FN_4O_4S$



704298: C32H40N4O5S



704299: C30H36N2O4

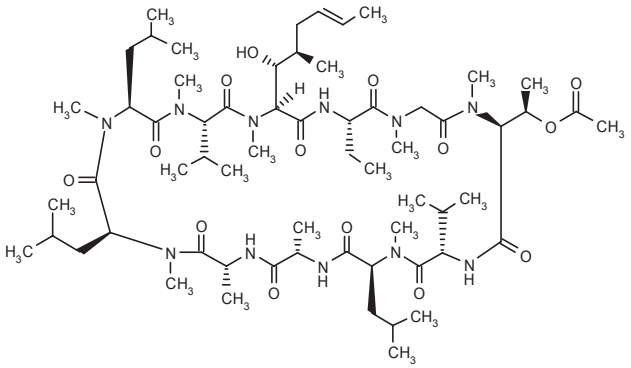
SOURCE – Istituto di Ricerche di Biologia Molecolare P. Angeletti, Pomezia (IT).

REFERENCES

1. Narjes, F. et al. (Istituto di Ricerche di Biologia Molecolare P. Angeletti SpA) *Macrocyclic and 7-aminoalkyl-substituted benzoxazocines for treatment of hepatitis C infections*. WO 2010082050.

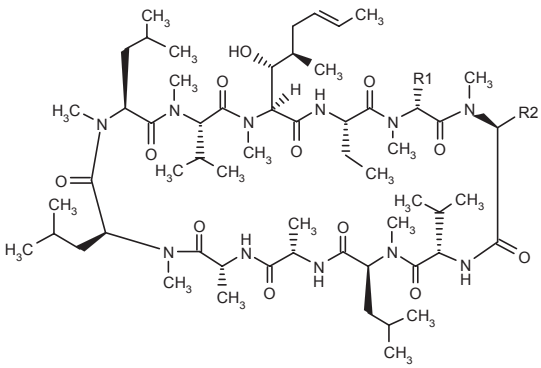
705281

Cyclo[[3(*R*)-hydroxy-4(*R*)-methyl-2(*S*)-(methylamino)-6(*E*)-octenoyl]-L-2-aminobutyryl-*N*-methylglycyl-*O*-acetyl-*N*-methyl-L-threonyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl]



C62H109N11O14; Mol wt: 1232.5942

ACTION – Cephalosporin analogue potentially useful for the treatment of hepatitis C infections. Further applications include hepatitis B, hepatitis A and HIV infections. Related compounds include:



Compound	R1	R2	Formula
705286	H	(R)-CH(Me)OCH2CH=CHPh	$C_{69}H_{115}N_{11}O_{13}$
705288	H	4-morpholinyl-CH2CH=CHCH2OCH(Me)	$C_{68}H_{120}N_{12}O_{14}$
705289	H	(R)-CH(Me)O(CH2)4NH2	$C_{64}H_{116}N_{12}O_{13}$
705290	Me	(R)-4-morpholinyl-CO2(CH2)4OCH(Me)	$C_{70}H_{124}N_{12}O_{16}$
705291	Me	1-Pip-(CH2)4OCH(Me)	$C_{70}H_{126}N_{12}O_{13}$
705293	Me	(R)-4-CF3-PhN(Me)(CH2)4OCH(Me)	$C_{73}H_{123}F_3N_{12}O_{13}$
705295	Me	(R)-CH(Me)O(CH2)4OH	$C_{65}H_{117}N_{11}O_{14}$

SOURCE – Enanta Pharmaceuticals.

REFERENCES

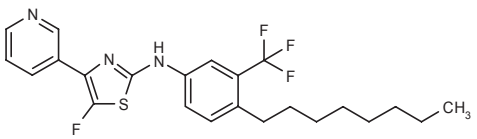
1. Or, Y.S. et al. (Enanta Pharmaceuticals, Inc.) *Cyclosporin analogues for preventing or treating hepatitis C infection*. US 2010196316, WO 2010088573.

ACH-1095[1-5]

444809

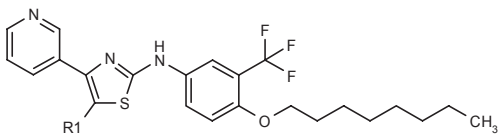
5-Fluoro-*N*-[4-octyl-3-(trifluoromethyl)phenyl]-4-(3-pyridyl)thiazol-2-amine

ACH-0141095
GS-9525



C23H25F4N3S; Mol wt: 451.5230

ACTION – Hepatitis C virus (HCV) NS3/NS4A protease inhibitor (EC_{50} = 0.038 μM) that displayed low cytotoxicity in rat hepatocytes and cancer cell lines (IC_{50} = 9.4 and > 10 μM, respectively) and low activity against cytochrome CYP450 isoenzymes (IC_{50} = 24.1, 32.5 and > 50 μM, respectively, for 3A4, 2C9 and 2D6) and the hERG channel (0.8% inhibition at 3 μM). Compound 30 and 100 mg/kg p.o. was safe and well tolerated on repeated dosing for 7 days in rats and dogs and did not induce alterations in food consumption, body weight, histology or clinical chemistry. Other related compounds are:



Compound	R1	Formula
ACH-0199 [706250][1,3]	H	$C_{23}H_{26}F_3N_3OS$
ACH-0140995 [706252][1,3]	F	$C_{23}H_{25}F_4N_3OS$

SOURCES – Achillion; Gilead.

REFERENCES

1. Wang, X. et al. (Achillion Pharmaceuticals, Inc.) *Heteroaryl substituted thiazoles and their use as antiviral agents*. CN 101801964, EP 2164846, JP 2010528019, WO 2008147557.

2. Gaudieri, S. et al. *Hepatitis C virus drug resistance and immune-driven adaptations: Relevance to new antiviral therapy*. Hepatology 2009, 49(4): 1069.

3. Phadke, A. et al. *HCV NS4A antagonists*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 257.

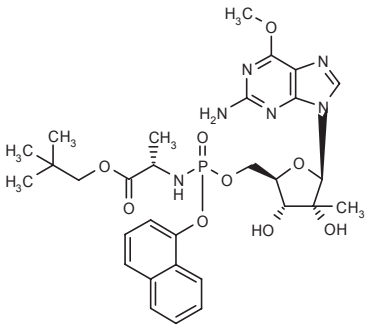
4. *Gilead and Achillion advance NS4A antagonist collaboration*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2007, Feb 13.

INX-08189

677790

2-Amino-6-methoxy-9-[2-*C*-methyl-5-[*O*-[*O*-(2,2-dimethylpropyl)-L-alanino](naphthalen-1-yloxy)phosphoryl]-β-D-ribofuranosyl]-9*H*-purine

INX-189



C30H39N6O9P; Mol wt: 658.6392

ACTION- Phosphoramidate nucleoside analogue that inhibits hepatitis C virus (HCV) NS5B (EC_{50} = 0.01 μM; EC_{90} = 0.04 μM in HCV 1b replicon assays) with low cytotoxicity against Huh-7 cells (CC_{50} = 7 μM); it is converted to the active triphosphate in hepatocytes. Compound has progressed to clinical trials for the treatment of chronic HCV infection.

SOURCES – Cardiff University, Cardiff (GB); Inhibitex.

REFERENCES

1. Chamberlain, S. et al. (University College Cardiff Consultants Ltd.;Inhibitex, Inc.) *Phosphoramidate derivatives of guanosine nucleoside compounds for treatment of viral infections*. WO 2010081082.

2. Hutchins, J. et al. *In vitro activity and in vivo pharmacokinetics of highly potent phosphoramidate nucleoside analogue inhibitors of hepatitis C NS5B*. Antivir Res 2009, 82(2): Abst 42.

3. Kolykhalov, A. et al. *In vitro characterization of INX-189, a highly potent phosphoramidate nucleoside analogue inhibitor of HCV*. Glob Antivir J 2009, 5(Suppl. 1): Abst 101.

4. McGuigan, C. et al. *Design, synthesis and evaluation of a novel double pro-drug: INX-08189. A new clinical candidate for hepatitis C virus*. Bioorg Med Chem Lett 2010, 20(16): 4850.

5. Patti, J. et al. *Pharmacological properties and in vitro characterization of INX-189, a liver targeted phosphoramidate nucleoside analogue inhibitor of NS5b*. Hepatology 2009, 50(Suppl. 4): Abst 1611.

6. *A study of the safety and pharmacokinetics of single ascending oral doses of INX-08189 in healthy subjects (NCT01159808)*. ClinicalTrials.gov Web Site 2010, July 25.

7. *Inhibitex initiates clinical trials of INX-189 in HCV infections*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2010, May 18.

8. *Inhibitex presents update on development of SA3Ag vaccine, FV-100 and INX-189*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2010, Jan 13.

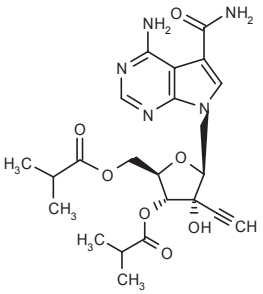
9. *Phase Ia trial of INX-08189 completed in chronic hepatitis C*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2010, Sept 2.

10. *Trials begin on hepatitis C drug*. Cardiff University Press Release 2010, May 14.

NITD-203[2-4]

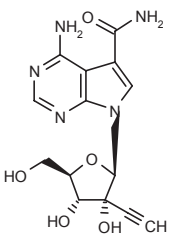
701621

4-Amino-7-(2-*C*-ethynyl-3,5-di-*O*-isobutyryl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide



C22H27N5O7; Mol wt: 473.4791

ACTION – Prodrug of **NITD-449**, a dengue virus RNA-directed RNA polymerase NS5 inhibitor (EC_{50} < 1 μM against all four serotypes in A549 and human peripheral blood mononuclear cells), with no cytotoxicity at up to 25 μM and superior potency compared to the parent drug. Doses of 3, 10 and 25 mg/kg p.o. b.i.d. reduced peak viremia in DENG-2-infected mice by 2.7-, 4.4- and 30-fold, respectively.



NITD-449 [701623][1-4]: C14H15N5O5

SOURCE – Novartis.

REFERENCES

1. Chen, Y.-L. et al. (Novartis AG) *New antiviral modified nucleosides*. WO 2010015637.

2. Chen, Y.L. et al. (Novartis AG) *New antiviral modified nucleosides*. US 2010144655, WO 2010015643.

3. Chen, Y.-L. et al. *Inhibition of dengue virus by an ester produg of an adenosine analog*. Antimicrob Agents Chemother 2010, 54(7): 2932.

4. Chen, Y.L. et al. *Inhibition of dengue virus by an ester prodrug of an adenosine analog*. Antimicrob Agents Chemother 2010, 54(8): 3255.

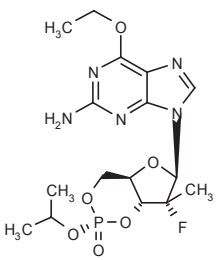
PSI-352938

664407

1-(2-Amino-6-ethoxy-9*H*-purin-9-yl)-2-fluoro-2-*C*-methyl-1,2-dideoxy-β-D-ribofuranose 3,5-cyclic [P(*R*)]-isopropylphosphate

Phosphoric acid [P(*R*)]-1-(2-amino-6-ethoxy-9*H*-purin-9-yl)-2-fluoro-2-*C*-methyl-β-D-ribofuranose-3,5-diyl isopropyl triester

PSI-938



C16H23FN5O6P; Mol wt: 431.3559

ACTION – Cyclic phosphate prodrug that inhibits hepatitis C virus (HCV) NS5B (EC_{50} = 0.19 and 0.11 μM, respectively, and EC_{90} = 0.55 and 1.08 μM, respectively, in HCV 1b and 1a replicon assays) with low cytotoxicity (CC_{50} > 100 μM) against Huh-7, Hep G2, pancreas BxPC3 and leukemia CEM cells. Phase Ib clinical trials are ongoing.

SOURCE – Pharmasset.

REFERENCES

1. Chun, B.-K. et al. (Pharmasset, Inc.) *Synthesis of purine nucleosides*. WO 2010075554.

2. Du, J. et al. (Pharmasset, Inc.) *Nucleoside cyclicphosphates*. WO 2009152095.

3. Lam, A.M. et al. *Novel 2'-F-2'-C-methylpurine nucleotide analogs are active inhibitors of HCV replication and lack cross-resistance with other nucleos(t)ide analogs*. Annu Meet Am Assoc Study Liver Dis 2010, Abst.

4. Lam, A.M. et al. *Selection and characterization of hepatitis C virus replicons using combination of NS3 protease and NS5B non-nucleoside inhibitors or combination of NS5B nucleotide inhibitors*. Int HIV & Hepat Virus Drug Resist Workshop & Curativ Strategies (June 8-12, Dubrovnik) 2010, Abst.

5. Reddy, P.G. et al. *Cyclic phosphate produgs of 2'-deoxy-2'-fluoro-2'-c-methyl nucleoside analogs as inhibitors of HCV NS5B polymerase*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 123.

6. Sofia, M.J. et al. *Discovery of PSI-352938 and PSI-353661: Purine nucleotide prodrugs for the treatment of HCV*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 19.

7. Zennou, V. et al. *Combination of two complementary nucleotide analogues PSI-7977 and PSI-938 effectively clears wild type and NS5B:S282T HCV replicons - Comparison with combinations of other antiviral compounds*. J Hepatol 2010, 52(Suppl. 1): Abst 1034.

8. *Events & presentations: PSI-7977 Update*. Pharmasset Web Site 2010, May 4.

9. *Pharmasset advances PSI-938 to the clinic for hepatitis C*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2010, April 12.

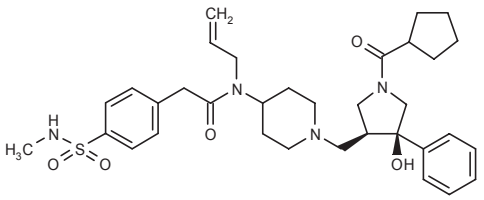
10. *Pharmasset begins phase Ib PSI-938 trial in chronic hepatitis C*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2010, July 30.

11. *Pharmasset nominates PSI-938 as development candidate for HCV infection*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2009, July 8.

AIDS MEDICINES

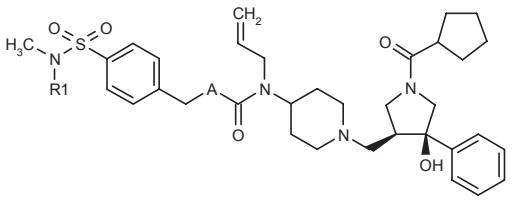
667191*

N-Allyl-*N*-[1-[1-(cyclopentylcarbonyl)-4(*R*)-hydroxy-4-phenylpyrrolidin-3(*S*)-ylmethyl]piperidin-4-yl]-2-[4-[*N*-methylsulfamoyl]-phenyl]acetamide



C34H46N4O5S; Mol wt: 622.8180

ACTION – Chemokine CCR5 receptor antagonist (IC_{50} = 1.53 nM in GTPγS binding assays) that displayed antiviral activity against R5-tropic HIV-1 strains (EC_{50} < 0.3 nM) in peripheral blood mononuclear cells, with selectivity over X4-tropic and R5/X4-tropic strains (EC_{50} > 1000 nM for both) and the hERG channel (34.1% at 10 μM). Other related compounds are:



Compound	R1	A	Formula
667199**	H	NH	$C_{34}H_{47}N_5O_5S$
667741	Me	bond	$C_{35}H_{48}N_4O_5S$
667750	Me	NH	$C_{35}H_{49}N_5O_5S$

SOURCES – Avexa; Shanghai TargetDrug.

REFERENCES

1. Chen, L. et al. (Shanghai TargetDrug Ltd.;Avexa Ltd.) *Pyrrolidine-based compounds*. WO 2009089659.

2. Chen, L. et al. (Shanghai TargetDrug Ltd.;Avexa Ltd.) *Pyrrolidine-based compounds*. WO 2009092293.

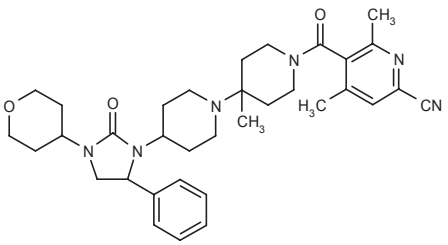
3. Ben, L. et al. *Studies on the structure-activity relationship of 1,3,3,4-tetra-substituted pyrrolidine embodied CCR5 receptor antagonists. Part 1: Tuning the N-substituents*. Bioorg Med Chem Lett 2010, 20(14): 4012.

*Identified compound **667191** (see **667183**) Drug Data Rep 2009, 031(08): 0800.

Identified compound **667199 (see **667183**) Drug Data Rep 2009, 031(08): 0800.

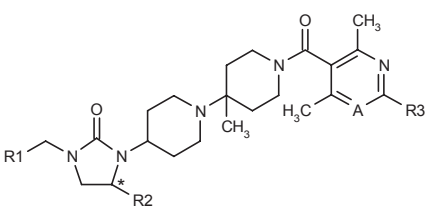
698620

4,6-Dimethyl-5-[4'-methyl-4-[2-oxo-5-phenyl-3-(tetrahydropyran-4-yl)imidazolidin-1-yl]-1,4'-bipiperidin-1'-ylcarbonyl]pyridine-2-carbonitrile



C34H44N6O3; Mol wt: 584.7516

ACTION – Chemokine CCR5 receptor antagonist (IC_{50} = 21 nM) that displayed antiviral activity against HIV-1 (IC_{50} = 7 nM in HeLa cells expressing CD4, CCR5 and CXCR4 receptors), with selectivity over the hERG channel (IC_{50} = of 3.5 μM). Oral bioavailabilty was 23 and 42%, respectively, in rats and monkeys. Other related compounds are:



Compound	R1	R2	R3	A	*Isomer	Formula
698618	4-THP	2-Pyr	CN	CH	R	$C_{34}H_{45}N_7O_3$
698619	trans-4-EtO-cyclohexyl	Ph	H	N	R	$C_{36}H_{52}N_6O_3$
698621	4-THP	Ph	H	N	R	$C_{33}H_{46}N_6O_3$

SOURCE – Roche.

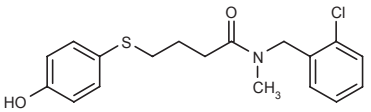
REFERENCES

1. Gabriel, S.D. et al. (F. Hoffmann-La Roche AG) *Heterocyclic antiviral compounds*. US 2009028818, WO 2009013171.

2. Rotstein, D.M. et al. *Synthesis, SAR and evaluation of [1,4']-bipiperidinyl-4-yl-imidazolidin-2-one derivatives as novel CCR5 antagonists*. Bioorg Med Chem Lett 2010, 20(11): 3219.

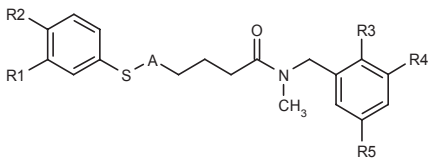
701522

N-(2-Chlorobenzyl)-4-(4-hydroxyphenylsulfanyl)-*N*-methylbutyramide



C18H20ClNO2S; Mol wt: 349.8750

ACTION – HIV integrase inhibitor that suppressed the production of caspid antigen CA p24 in HIV-infected cells with an EC_{50} of > 5 µM in a luciferase reporter gene assay. Related compounds include:



Compound	R1	R2	R3	R4	R5	A	Formula
701526	H	OH	OMe	H	H	CH2	$C_{20}H_{25}NO_3S$
701527	OH	H	OMe	H	H	bond	$C_{19}H_{23}NO_3S$
701529	H	OH	4-(4-morpholinyl--CH2CH2)-1-Piz	H	H	bond	$C_{28}H_{40}N_4O_3S$
701531	H	OH	OMe	Cl	Cl	bond	$C_{19}H_{21}Cl_2NO_3S$
701533	H	F	i-PrO	H	F	bond	$C_{21}H_{25}F_2NO_2S$
701534	H	CO2Me	OMe	H	H	bond	$C_{21}H_{25}NO_4S$
701535	H	OH	1,2,3,6-tetrahydro--4-Pyr	H	H	bond	$C_{23}H_{28}N_2O_2S$

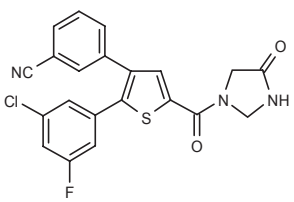
SOURCES – CellVir; CNRS, Paris (FR); INSERM, Paris (FR).

REFERENCES

1. Emiliani, S. et al. (CellVir SAS;INSERM (Institut National de la Sante et de la Recherche Medical;Centre National de la Recherche Scientifique) *Novel substituted aryl derivatives, their process of preparation and their therapeutical uses as anti-HIV agents.* EP 2196453, WO 2010066847.

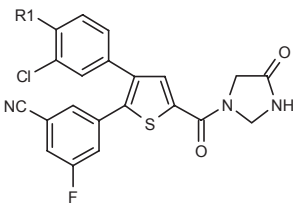
701880

3-[2-(3-Chloro-5-fluorophenyl)-5-(4-oxoimidazolidin-1-ylcarbonyl)-thien-3-yl]benzonitrile



C21H13ClFN3O2S; Mol wt: 425.8630

ACTION – Anti-HIV agent that inhibited the replication of wild-type HIV-1 LAI in H9 cells with an EC_{50} of 9 nM, as well as the replication of wild-type HIV-1 NL4-3 and mutant K103N Y181C in MT4-7F2 cells with EC_{50} values of 1 and 45 nM, respectively. Related compounds include:



Compound	R1	Formula
701873	H	$C_{21}H_{13}ClFN_3O_2S$
701877	F	$C_{21}H_{12}ClF_2N_3O_2S$

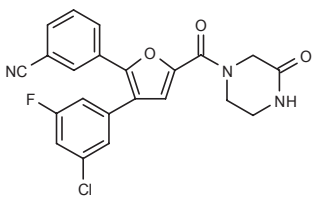
SOURCE – AiCuris.

REFERENCES

1. Thede, K. et al. (AiCuris GmbH & Co. KG) *Substituted (thiophenyl-carbonyl)imidazolidinones, and use thereof.* DE 102008062863, WO 2010075962.

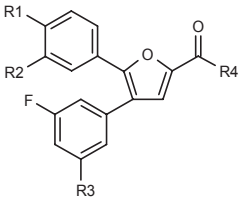
701884

3-[3-(3-Chloro-5-fluorophenyl)-5-(3-oxopiperazin-1-ylcarbonyl)-furan-2-yl]benzonitrile



C22H15ClFN3O3; Mol wt: 423.8240

ACTION – Anti-HIV agent that inhibited the replication of wild-type HIV-1 LAI in H9 cells with an EC_{50} of 7 nM, as well as the replication of wild-type HIV-1 NL4-3 and mutant K103N-Y181C in MT4-7F2 cells with EC_{50} values of 1 and 160 nM, respectively. Related compounds include:



Compound	R1	R2	R3	R4	Formula
701875	H	CN	CN	4-morpholinyl	$C_{23}H_{16}FN_3O_3$
701876	H	Cl	CN	3-oxo-1-Piz	$C_{22}H_{15}ClFN_3O_3$
701878	H	CN	Cl	1,1-dioxo-3-thiazolidinyl	$C_{21}H_{14}ClFN_2O_4S$
701879	F	Cl	Cl	1-oxo-3-thiazolidinyl	$C_{20}H_{13}Cl_2F_2NO_3S$
701881	H	CN	Cl	1-oxo-3-thiazolidinyl	$C_{21}H_{14}ClFN_2O_3S$

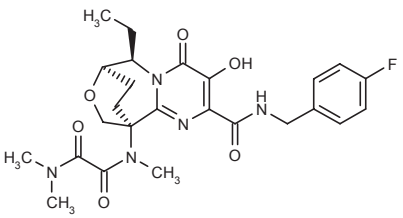
SOURCE – AiCuris.

REFERENCES

1. Thede, K. et al. (AiCuris GmbH & Co. KG) *Substituted furancarboxamides, and use thereof*. DE 102008062878, WO 2010075957.

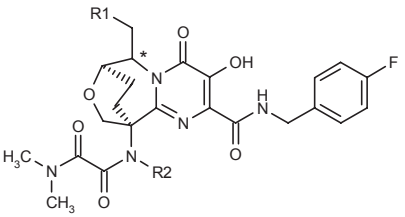
705231

anti-N^1-[6-Ethyl-2-[*N*-(4-fluorobenzyl)carbamoyl]-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydro-7,10-(epoxymethano)pyrimido[1,2-*a*]-azepin-10-yl]-N^1,N^2,N^2-trimethyloxamide isomer A

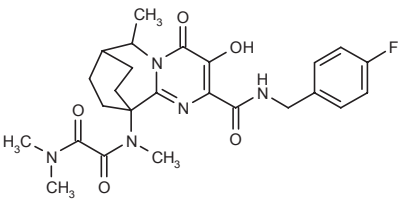


C25H30FN5O6; Mol wt: 515.5340

ACTION – HIV integrase inhibitor that suppressed the replication of HIV expressing wild-type HIV integrase and mutant N155H, Q148R, Y143R and G140S/Q148H integrase in HeLa P4-2 cell lines (IC_{50} = 8, 1, 1, 1 and 1 nM, respectively). It inhibited acute HIV-1 infection of T-lymphoid cells with IC_{95} value of 7.9 nM. Compound exhibited no cytotoxicity at up to 0.5 µM. Related compounds include:



Compound	R1	R2	*Isomer	Formula
705235	Me	H	syn	$C_{24}H_{28}FN_5O_6$
705236	H	Me	syn	$C_{24}H_{28}FN_5O_6$
705237	H	Me	anti	$C_{24}H_{28}FN_5O_6$
705238	H	H	syn	$C_{23}H_{26}FN_5O_6$
705240	H	H	anti	$C_{23}H_{26}FN_5O_6$



705233: C25H30FN5O5

SOURCE – Merck & Co.

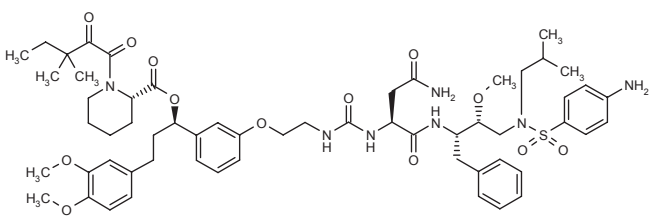
REFERENCES

1. Venkatraman, S. et al. (Merck & Co., Inc.) *Bridged compounds as HIV integrase inhibitors*. WO 2010088167.

APX-9

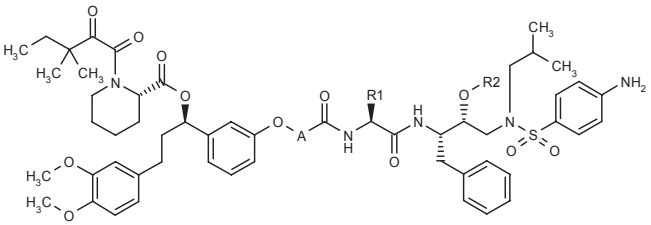
702052

N^1-[4-[*N*-(4-Aminophenylsulfonyl)-*N*-isobutylamino]-3(*R*)-methoxy-1-phenylbutan-2(*S*)-yl]-N^2-[*N*-[2-[3-[3-(3,4-dimethoxyphenyl)-1(*R*)-[1-(3,3-dimethyl-2-oxopentanoyl)piperidin-2(*S*)-ylcarbonyloxy]propyl]phenoxy]ethyl]carbamoyl]-L-aspartamide



C58H79N7O13S; Mol wt: 1114.3520

ACTION – HIV protease inhibitor (IC_{50} = 1.8 nM) that reduced the growth of T-cell-tropic HIV-1 LAI-infected CEM-T4 cells with an IC_{50} of 2.3 nM. Related compounds include:



Compound	R1	R2	A	Formula
APX-5 [702057]	i-Pr	H	-CH2-	$C_{57}H_{77}N_5O_{12}S$
APX-7 [702063]	CH2CONH2	Me	-CH2-	$C_{57}H_{76}N_6O_{13}S$
APX-10 [702064]	i-Pr	H	-CH2CH2NH-	$C_{58}H_{80}N_6O_{12}S$

SOURCE – Amplyx Pharmaceuticals.

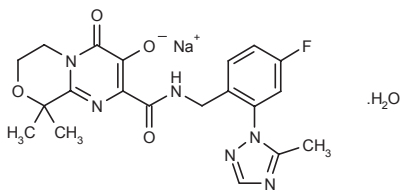
REFERENCES

1. Mutz, M. et al. (Amplyx Pharmaceuticals, Inc.) *Protease inhibitors*. WO 2010077317.

BMS-727740

676160

2-[*N*-[4-Fluoro-2-(5-methyl-1*H*-1,2,4-triazol-1-yl)benzyl]carbamoyl]-9,9-dimethyl-4-oxo-4,6,7,9-tetrahydropyrimido[2,1-c][1,4]oxazin-3-ol sodium salt hydrate



C20H22FN6NaO5; Mol wt: 468.4141

ACTION – HIV integrase inhibitor (IC_{50} = 10 nM; K_i = 2.7 nM) that suppressed HIV replication with an IC_{50} of 24 and 4.4 nM, respectively, with and without human serum albumin. Oral bioavailablitly was 66, 120 and 94%, respectively, in rats, dogs and monkeys.

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Choi, C.Y. and Ng, A.T.F. (Bristol-Myers Squibb Co.) *Crystalline form of N-[[4-fluoro-2-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl]methyl]-4,6,7,9-tetrahydro-3-hydroxy-9,9-dimethyl-4-oxo-pyrimido[2,1-c]-[1,4]oxazine-2-carboxamide, sodium salt monohydrate*. WO 2009120841.

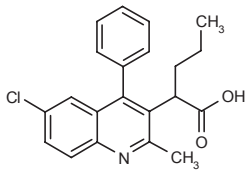
2. Naidu, B.N. et al. (Bristol-Myers Squibb Co.) *Bicyclic heterocycles as HIV integrase inhibitors*. EP 1749011, JP 2008501018, US 2005267105, US 7176196, WO 2005118593.

3. Walker, M.A. et al. *Discovery and preclinical evaluation of the HIV integrase inhibitor BMS-727740*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 135.

CX-4328

697793

2-(6-Chloro-2-methyl-4-phenylquinolin-3-yl)pentanoic acid



C21H20ClNO2; Mol wt: 353.8420

ACTION – Lens epithelium-derived growth factor-integrase interaction inhibitor (IC_{50} = 1.37 μM that reduced the HIV-1-induced cytopathic effect in MT-4 cells (EC_{50} = 2.35 μM), with low cytotoxicity (CC_{50} = 59.8 μM). Little or no crossresistance with raltegravir, zidovudine, efavirenz and plerixafor was observed.

SOURCES – Universität Basel, Basel (CH); Boehringer Ingelheim; Katholieke Universiteit Leuven, Leuven (BE).

REFERENCES

1. Tsantrizos, Y.S. et al. (Boehringer Ingelheim Pharma GmbH & Co. KG) *Inhibitors of human immunodeficiency virus replication*. EP 2019825, JP 2009537459, US 2008221159, WO 2007131350.

2. Christ, E. et al. *The LEDGINs: Rational design of first in class LEDFG/p75-integrase inhibitors with potent antiviral activiti*. 18th Int AIDS Conf (July 18-23, Vienna) 2010, Abst MOAA0105.

3. Christ, F. et al. *Rational design of small-molecule inhibitors of the LEDGF/p75-integrase interaction and HIV replication*. Nat Chem Biol 2010, 6(6): 442.

4. Desimmie, B.A. et al. *LEDGINs: First-in-class inhibitors of LEDGF/p75-integrase interaction and HIV replication*. 18th Int AIDS Conf (July 18-23, Vienna) 2010, Abst MOPE0022.

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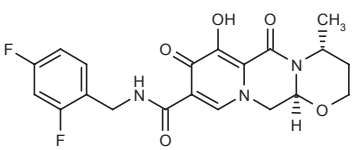
GSK-1349572

466915

(4*R*,12a*S*)-*N*-(2,4-Difluorobenzyl)-7-hydroxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]-oxazine-9-carboxamide

S/GSK-1349572
S-349572
1349572
572



C20H19F2N3O5; Mol wt: 419.3788

ACTION – HIV integrase inhibitor (IC_{50} = 2.7 nM in a strand transfer assay) giving IC_{50} values of 0.22-0.62, 0.87, 0.29 and 0.76 nM, respectively, against HIV-1 group M subtypes A-G, group O and HIV-2 isolates in peripheral blood mononuclear cells and monocyte-derived macrophages. Doses of 2-50 mg/day for 10 days were well tolerated in HIV-infected patients (N = 35) and plasma HIV-1 RNA declined by 1.51-2.46 log_{10} copies/mL after 11 days. In a phase II trial single or repeated doses of 2-100 mg in 166 subjects were well tolerated, with headache, diarrhea, nausea, dizziness and vomiting in a few subjects. Phase II clinical trials are under way.

SOURCES – GlaxoSmithKline; Shionogi; ViiV Healthcare.

REFERENCES

1. Johns, B.A. et al. (Shionogi & Co. Ltd.) *Polycyclic carbamoylpyridone derivative having HIV integrase inhibitory activity*. EP 1874117, JP 2008540343, JP 2009079058, US 2009318421, WO 2006116764.

2. Johns, B.A. et al. (Shionogi & Co. Ltd.;GlaxoSmithKline Inc.) *Processes and intermediates for carbamoylpyridone HIV integrase inhibitors*. WO 2010068262.

3. Yoshida, H. et al. (Shionogi & Co. Ltd.;GlaxoSmithKline Inc.) *Synthesis of carbamoylpyridone HIV integrase inhibitors and intermediates*. WO 2010068253.

4. Arribas, J. et al. *Once-daily S/GSK1349572 as part of combination therapy in antiretroviral naïve adults: rapid and potent antiviral responses in the interim 16-week analysis from SPRING-1 (ING112276)*. 18th Int AIDS Conf (July 18-23, Vienna) 2010, Abst THLBB205.

5. Clotet, B. et al. *HIV integrase genotypic and phenotypic changes between Day1 and Day11 in subjects with raltegravir (RAL) resistant HIV treated with S/GSK1349572: Results of VIKING study (ING112961)*. 18th Int AIDS Conf (July 18-23, Vienna) 2010, Abst TUPE0130.

6. Chen, S. et al. *S/GSK1349572 thorough QT/QTc study: A single supratherapeutic dose of S/GSK1349572 does not prolong the QTcF interval*. 50th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 12-15, Boston) 2010, Abst A1-2014.

7. Deanda, F. et al. *Structural rationale for slow S/GSK1349572 dissociation from wild type (WT) and raltegravir (RAL) resistant HIV-1 integrase (IN)*. 50th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 12-15, Boston) 2010, Abst H-1166.

8. Eron, J. et al. *Activity of a next generation integrase inhibitor (INI), S/GSK1349572, in subjects with HIV exhibiting raltegravir resistance: Initial results of VIKING study (ING112961)*. 18th Int AIDS Conf (July 18-23, Vienna) 2010, Abst MOAB0105.

9. Fujiwara, T. et al. *Potent antiviral activity and well-characterized exposure-activity relationship of S/GSK1349572, anext generation integrase inhibitor (INI)*. HIV Med 2009, 10(Suppl. 2): Abst PE7.2/4.

10. Johns, B. et al. *The discovery of S/GSK1349572: A once daily next generation integrase inhibitor with a superior resistance profile*. 17th Conf Retroviruses Opportunistic Infect (CROI) (Feb 16-19, San Francisco) 2010, Abst 55.

11. Lalezari, J. et al. *Potent antiviral activity of S/GSK1349572, a next generation ointegrase inhibitor (INI), in INI-naïve HIV-1-infected patients*. 5th IAS Conf HIV Pathog Treat Prev (July 19-22, Cape Town) 2009, Abst TUAB105.

12. Lou, Y. et al. *Meta-analysis of safety for short-term dosing of an HIV integrase inhibitor, S/GSK1349572, from seven clinical studies*. 49th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 12-15, San Francisco) 2009, Abst H-931.

13. Min, S. et al. *Pharmacokinetics (PL) and safety in healthy sibjects of S/GSK1349572, a next generation, once-daily HIV integrase inhibitor (INI)*. 5th IAS Conf HIV Pathog Treat Prev (July 19-22, Cape Town) 2009, Abst WEPEA099.

14. Min, S. et al. *Pharmacokinetics and safety of S/GSK1349572, a next-generation HIV integrase inhibitor, in healthy volunteers*. Antimicrob Agents Chemother 2010, 54(1): 254.

15. Patel, P. et al. *S/GSK1349572, a next generation HIV integrase inhibitor, pharmacokinetics are not affected by omeprazole in healthy adults*. 50th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 12-15, Boston) 2010, Abst H-934.

16. Sato, A. et al. *In vitro passage of drug resistant HIV-1 against a next generation integrase inhibitor (INI), S/GSK1349572*. 49th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 12-15, San Francisco) 2009, Abst H-932.

17. Sato, A. et al. *S/GSK1349572 is a potent next generation HIV integrase inhibitor*. 5th IAS Conf HIV Pathog Treat Prev (July 19-22, Cape Town) 2009, Abst WEPEA097.

18. Sato, A. et al. *S/GSK1349572 is a potent next-generation HIV integrase inhibitor*. HIV Med 2009, 10(Suppl. 2): Abst PE7.1/1.

19. Song, I. et al. *Evaluation of antacid and multivitamin (MVI) effects on S/GSK1349572 pharmacokinetics (PK) in healthy subjects*. 49th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 12-15, San Francisco) 2009, Abst A1-1305.

20. Song, I. et al. *Lack of interaction between the HIV integrase inhibitor, S/GSK1349572, and tenofovir disoproxil fumarate (TDF) in healthy subjects*. 49th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 12-15, San Francisco) 2009, Abst A1-1303.

21. Song, I. et al. *Pharmacokinetic (PK) and pharmacodynamic (PD) relationship of S/GSK1349572, a next generation integrase inhibitor (INI), in HIV-1 infected patients*. 5th IAS Conf HIV Pathog Treat Prev (July 19-22, Cape Town) 2009, Abst WEPEB250.

22. Song, I. et al. *The effect of ritonavir-boosted protease inhibitors (PIs) on the HIV integrase inhibitor, S/GSK1349572, in healthy subjects*. 49th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 12-15, San Francisco) 2009, Abst A1-1304.

23. Underwood, M. et al. *Activity of the next generation integrase inhibitor S/GSK1349572 and two fi rst generation inhibitors across a broad panel of HIV subtype isolates in PBMCs and MDMs*. 18th Int AIDS Conf (July 18-23, Vienna) 2010, Abst MOPE0032.

24. Underwood, M. et al. *S/GSK1349572: A next generation integrase inhibitor with activity against integrase inhibitor resistant clinical isolates from patients experiencing virologic failure while on raltegravir therapy*. 5th IAS Conf HIV Pathog Treat Prev (July 19-22, Cape Town) 2009, Abst WEPEA098.

25. Vavro, C.L. et al. *Polymorphisms at position 101 and 124 in the HIV-1 integrase (IN) gene: Lack of effects on in vitro susceptibility to S/GSK1349572*. 50th Intersci Conf Antimicrob Agents Chemother (ICAAC) (Sept 12-15, Boston) 2010, Abst H-935.

26. *A clinical research study for assessing the effectiveness of the new integrase inhibitor GSK1349572 in HIV-infected persons with prior antiretroviral treatment and resistance to raltegravir (NCT00950859)*. ClinicalTrials.gov Web Site 2010, July 20.

27. *A dose ranging trial of GSK1349572 and 2 NRTI in HIV-1 infected, therapy naive subjects (ING112276) (NCT00951015)*. ClinicalTrials.gov Web Site 2009, Aug 21.

28. *A study to evaluate the effect of antacid and multivitamin and mineral tablet on the study drug GSK1349572 (DDI) (NCT00858455)*. ClinicalTrials.gov Web Site 2010, July 22.

29. *Drug interaction study between GSK1349572 and Tipranavir/Ritonavir in healthy volunteers (ING) (NCT01068925)*. ClinicalTrials.gov Web Site 2010, Feb 25.

30. *GSK1349572 drug interaction study with atazanavir/ritonavir and atazanavir (NCT00883935)*. ClinicalTrials.gov Web Site 2009, April 20.

31. *GSK1349572 drug interaction study with efavirenz (NCT01098526)*. ClinicalTrials.gov Web Site 2010, July 22.

32. *GSK1349572 drug interaction study with etravirine (NCT00774111)*. ClinicalTrials.gov Web Site 2008, Oct 30.

33. *GSK1349572 drug interaction study with protease inhibitors (NCT00774735)*. ClinicalTrials.gov Web Site 2010, July 22.

34. *GSK1349572 drug interaction with etravirine and either darunavir/ritonavir or lopinavir/ritonavir (NCT00867152)*. ClinicalTrials.gov Web Site 2010, July 22.

35. *GSK1349572 drug interaction with tenofovir (NCT00726336)*. ClinicalTrials.gov Web Site 2010, July 22.

36. *GSK1349572 first time in human study (NCT00555035)*. ClinicalTrials.gov Web Site 2008, March 25.

37. *GSK1349572 mass balance study (NCT00828763)*. ClinicalTrials.gov Web Site 2009, April 1.

38. *GSK1349572 proton pump inhibitor drug interaction and supratherapeutic dose study (NCT00942136)*. ClinicalTrials.gov Web Site 2009, July 20.

39. *GSK1349572 relative bioavailability study (NCT01098513)*. ClinicalTrials.gov Web Site 2010, April 8

40. *GSK1349572 repeat dose escalation and relative bioavailability study (NCT00631592)*. ClinicalTrials.gov Web Site 2008, April 7.

41. *Phase IIa dose-ranging study of GSK1349572 in HIV-1 infected adult (NCT00708110).* ClinicalTrials.gov Web Site 2008, July 28.

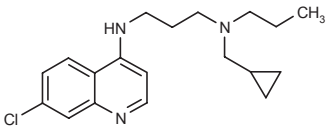
42. *Shionogi-GlaxoSmithKline revises criteria for S/GSK-1349572 AIDS trial.* Thomson Reuters Drug News (formerly DailyDrugNews.com) 2009, Aug 18.

43. *Study to assess cardiac conduction of GSK1349572 (NCT00996021).* ClinicalTrials.gov Web Site 2009, Oct 22.

TREATMENT OF PROTOZOAL DISEASES

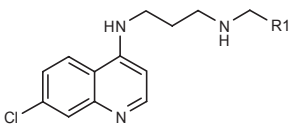
698323

N'-(7-Chloroquinolin-4-yl)-*N*-(cyclopropylmethyl)-*N*-propyl-propane-1,3-diamine



C19H26ClN3; Mol wt: 331.8830

ACTION – Antimalarial agent that showed MIC values of 14.5 and 17.3 nM against chloroquine-sensitive and -resistant strains of *Plasmodium falciparum*, with low cytotoxicity against rat hepatocytes (TC_{50} = 40 and 30 µM, respectively, in MTT and lactate dehydrogenase assays). Compound exhibited good oral bioavailability (relative bioavailability > 2.34-fold that of chloroquine) in mice. Other related compounds are:



Compound	R1	Formula
698322	3-MeO-2-OH-Ph	$C_{20}H_{22}ClN_3O_2$
698324	1,3-benzodioxol-4-yl	$C_{20}H_{20}ClN_3O_2$

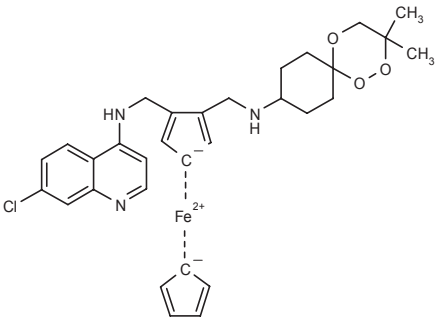
SOURCES – University of California, San Francisco, San Francisco, CA (US); SRI International, Menlo Park, CA (US); St. Jude Children's Research Hospital, Memphis, TN (US).

REFERENCES

1. Ray, S. et al. *Development of a new generation of 4-aminoquinoline antimalarial compounds using predictive pharmacokinetic and toxicology models.* J Med Chem 2010, 53(9): 3685.

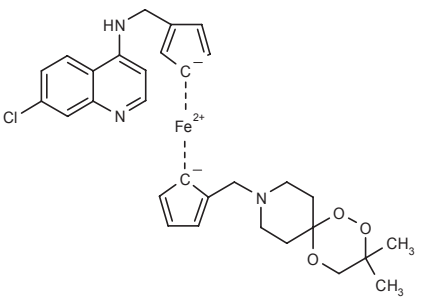
698485

3-(7-Chloroquinolin-4-ylaminomethyl)-4-(3,3-dimethyl-1,2,5-trioxaspiro[5.5]undecan-9-ylaminomethyl)ferrocene

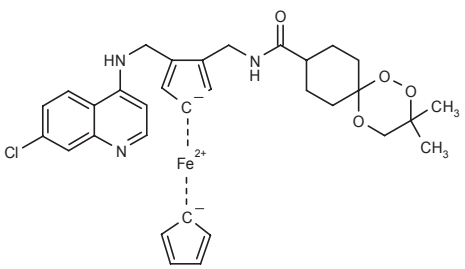


C31H36ClFeN3O3; Mol wt: 589.9340

ACTION – Hybrid antimalarial trioxaferroquine (IC_{50} = 20 and 17 nM, respectively, against chloroquine-resistant FcB1 and FcM29 strains of *Plasmodium falciparum*) that significantly reduced parasitemia in mice infected with *Plasmodium vinckei petteri* at doses of 10-25 mg/kg/day p.o. after 4 days (2/5 cures at the highest dose). Other related compounds are:



698468: C30H34ClFeN3O3



698483: C32H36ClFeN3O4

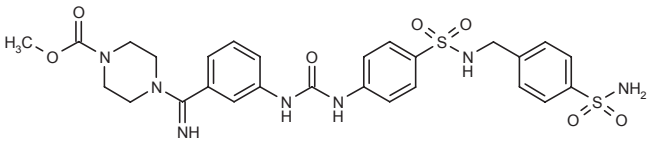
SOURCE – Palumed.

REFERENCES

1. Bellot, F. et al. *Trioxaferroquines as new hybrid antimalarial drugs.* J Med Chem 2010, 53(10): 4103.

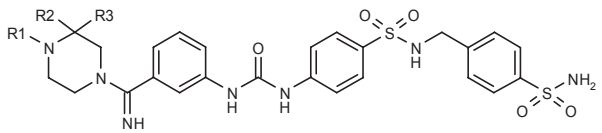
705022

4-[1-Imino-1-[3-[3-[4-[*N*-(4-sulfamoylbenzyl)sulfamoyl]phenyl]-ureido]phenyl]methyl]piperazine-1-carboxylic acid methyl ester



C27H31N7O7S2; Mol wt: 629.7080

ACTION – Compound that displayed antiprotozoal activity against *Plasmodium falciparum* Dd2 strain (IC_{50} = 0.02 µM). Other representative compounds are:



Compound	R1	R2	R3	Formula
705023	Bu	H	H	$C_{29}H_{37}N_7O_5S_2$
705025	Pr	H	H	$C_{28}H_{35}N_7O_5S_2$
705026	COEt	H	H	$C_{28}H_{33}N_7O_6S_2$
705027	Bu	-O-		$C_{29}H_{35}N_7O_6S_2$
705028	cyclopropyl-CH2	H	H	$C_{29}H_{35}N_7O_5S_2$

SOURCE – 4SC.

REFERENCES

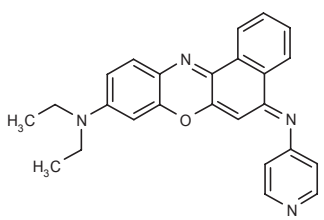
1. Pegoraro, S. (4SC AG) *Sulfamoyl-phenyl-ureido benzamidine-derivatives as antimalarial agents*. US 2010197640, WO 2010086177.

SSJ-183

680591

N,*N*-Diethyl-5-(pyridin-4-ylimino)-5*H*-benzo[*a*]phenoxazin-9-amine

SJM-01



C25H22N4O; Mol wt: 394.4684

ACTION – Antimalarial agent giving an IC_{50} of 0.0076 µM against *Plasmodium falciparum* K1 strain and showing good selectively over *Trypanosoma brucei rhodesiense*, *Trypansoma cruzi* and *Leishmania donovani* (IC_{50} = 36,000, 11,300 and 6500 nM, respectively). Oral bioavailability was 31% in rats. No lethality was detected in mice at doses up to 2000 mg/kg p.o. In mice infected with *Plasmodium berghei* a dose of 100 mg/kg/day p.o. produced a significant reduction in parasitemia.

SOURCES – Hoshi University, Shinagawa (JP); Swiss Tropical and Public Health Institute, Basel (CH); Synstar Japan (SSJ).

REFERENCES

1. Ihara, M. et al. (Swiss Tropical and Public Health Institute;Hoshi University;Synstar Japan Co., Ltd.) *Medicinal composition containing benzo[a]phenoxanthin compound as the active ingredient for preventing or treating protozoal disease*. WO 2009113569.

2. Arai, C. et al. *Development of novel benzo[a]phenoxazine derivative as antimalarial agent*. 28th Med Chem Symp (Nov 25-27, Tokyo) 2009, Abst 2P-02.

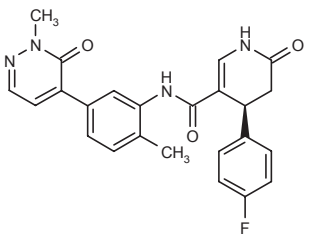
3. Ge, J.-F. et al. *Discovery of novel benzo[a]phenoxazine SSJ-183 as a drug candidate for malaria*. ACS Med Chem Lett 2010, Adv. Publication.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

TREATMENT OF ARTHRITIS

703641

4(*S*)-(4-Fluorophenyl)-*N*-[2-methyl-5-(2-methyl-3-oxo-2,3-dihydropyridazin-4-yl)phenyl]-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxamide

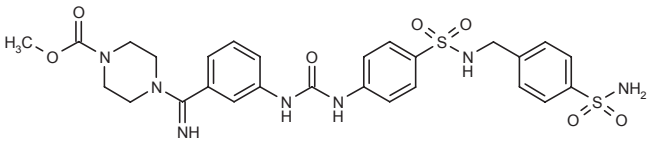


C24H21FN4O3; Mol wt: 432.4469

ACTION – Purinoceptor P2X7 ligand that displayed a pK_i value of 8.395 at P2X7 receptors, potentially useful for the treatment of arthritis. Related compounds include:

705022

4-[1-Imino-1-[3-[3-[4-[*N*-(4-sulfamoylbenzyl)sulfamoyl]phenyl]-ureido]phenyl]methyl]piperazine-1-carboxylic acid methyl ester



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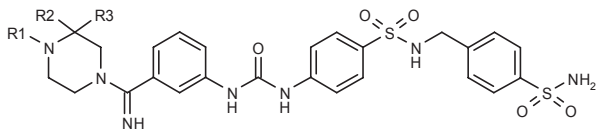
ACTION – Compound that displayed antiprotozoal activity against *Plasmodium falciparum* Dd2 strain (IC_{50} = 0.02 µM). Other representative compounds are:



Compound	R1	R2	R3	Formula
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705027	Bu	-O-		$C_{29}H_{35}N_7O_6S_2$
705028	cyclopropyl-CH2	H	H	$C_{29}H_{35}N_7O_5S_2$

SOURCE – 4SC.

REFERENCES

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SSJ-183

680591

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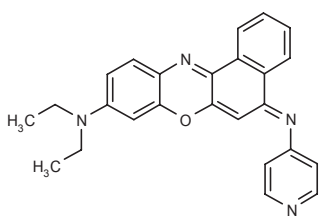
SJM-01



C25H22N4O; Mol wt: 394.4684

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SOURCES – Hoshi University, Shinagawa (JP); Swiss Tropical and Public Health Institute, Basel (CH); Synstar Japan (SSJ).

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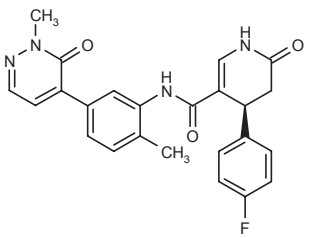
3. Ge, J.-F. et al. *Discovery of novel benzo[a]phenoxazine SSJ-183 as a drug candidate for malaria*. ACS Med Chem Lett 2010, Adv. Publication.

TREATMENT OF MUSCULOSKELETAL AND CONNECTIVE TISSUE DISEASES

TREATMENT OF ARTHRITIS

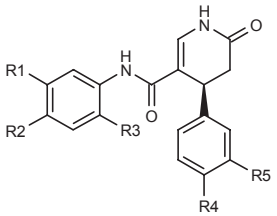
703641

4(*S*)-(4-Fluorophenyl)-*N*-[2-methyl-5-(2-methyl-3-oxo-2,3-dihydropyridazin-4-yl)phenyl]-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxamide



C24H21FN4O3; Mol wt: 432.4469

ACTION – Purinoceptor P2X7 ligand that displayed a pK_i value of 8.395 at P2X7 receptors, potentially useful for the treatment of arthritis. Related compounds include:



Compound	R1	R2	R3	R4	R5	Formula
703642	2-oxo-3-oxazolidinyl-CH2	Cl	Me	F	H	$C_{23}H_{21}ClFN_3O_4$
703643	5-Me-3-pyrazolyl	F	Me	F	H	$C_{23}H_{20}F_2N_4O_2$
703644	3-oxo-2,3-dihydro-4-pyridazinyl	H	Me	F	H	$C_{23}H_{19}FN_4O_3$
703646	4-thiazolyl	H	Me	F	H	$C_{22}H_{18}FN_3O_2S$
703651	5-Me-2-oxo-1,2-dihydro-1-Pyr	H	Me	F	H	$C_{25}H_{22}FN_3O_3$
703652	2-Me-3-oxo-2,3-dihydro-4-pyridazinyl	H	F	F	H	$C_{23}H_{18}F_2N_4O_3$
703653	2-Me-3-oxo-2,3-dihydro-4-pyridazinyl	H	Me	H	F	$C_{24}H_{21}FN_4O_3$

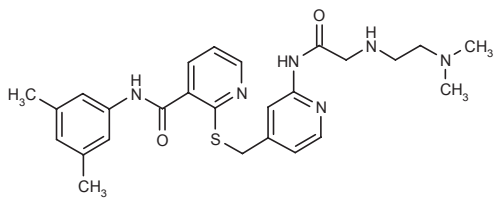
SOURCE – Roche.

REFERENCES

1. Berger, J. et al. (F. Hoffmann-La Roche AG) *Dihydropyridone amides as P2X7 modulators*. US 2010160384, WO 2010072607.

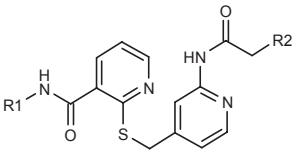
706266

2-[2-[2-[2-(Dimethylamino)ethylamino]acetamido]pyridin-4-ylmethylsulfanyl]-*N*-(3,5-dimethylphenyl)pyridine-3-carboxamide



C26H32N6O2S; Mol wt: 492.6360

ACTION – Orally available vascular endothelial growth factor receptor VEGFR-2 inhibitor that inhibited VEGF-induced proliferation of human umbilical vein endothelial cells (IC_{50} = 5.9 nM). Compound significantly inhibited adjuvant-induced arthritis in Lewis rats at a dose of 10 mg/kg/day p.o. over 21 days and laser-induced angiogenesis in a rat choroidal neovascularization model at a dose of 3 mg/kg p.o. It also showed tumor growth suppression in mice bearing B16 tumor xenografts at 100 mg/kg/day p.o. Potentially useful for the treatment of rheumatoid arthritis, cancer, age-related macular degeneration and diabetic retinopathy. Other related compounds are:



Compound	R1	R2	Formula
415743	4-(CF3O)-Ph	H	$C_{21}H_{17}F_3N_4O_3S$
415751	4-(CF3O)-Ph	OH	$C_{21}H_{17}F_3N_4O_4S$
415752	3,5-(Me)2-Ph	H	$C_{22}H_{22}N_4O_2S$
706264	3,5-(Me)2-Ph	Me	$C_{23}H_{24}N_4O_2S$

SOURCE – Santen.

REFERENCES

1. Honda, T. et al. (Santen Pharmaceutical Co., Ltd.) *Novel cyclic compound having 4-pyridylalkylthio group having (un)substituted amino introduced therein*. EP 1717229, JP 2006096739, US 2007149574, US 7544703, WO 2005085201.

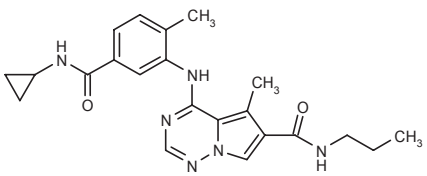
2. Tajima, H. et al. *Novel VEGFR2 inhibitors: Pyridylmethylthio derivatives with intramolecular nonbonded S-O interaction*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 66.

BMS-582949[1-14]

442604

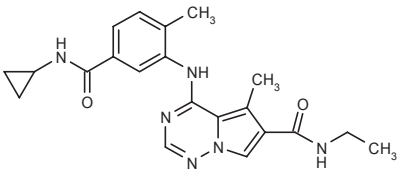
4-[5-(*N*-Cyclopropylcarbamoyl)-2-methylphenylamino]-5-methyl-*N*-propylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide

PS-540446



C22H26N6O2; Mol wt: 406.4808

ACTION – MAP kinase p38α inhibitor (IC_{50} = 13 nM) with > 2,000-fold selectivity over a panel of other kinases and 450-, 190- and 5-fold selectivity, respectively, over MAPK 9, RAF proto-oncogene and MAPK 11; it also inhibited TNF-α in human peripheral blood mononuclear cells with an IC_{50} of 50 nM. In mice compound showed an oral bioavailability of 90%. In a mouse model of lipopolysaccharide-induced inflammation compound 5 mg/kg p.o. significantly reduced serum TNF-α production. In clinical trials in healthy subjects and patients with rheumatoid arthritis multiple ascending doses of 10-600 mg/kg/day p.o. were safe and well tolerated. Phase II trials in patients with atherosclerosis are under way. Another representative compound is:



BMS-573298 [706405][2,6,7]: C21H24N6O2

SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Cann, R.O. et al. (Bristol-Myers Squibb Co.) *Process for preparing pyrrolotriazine aniline compounds useful as kinase inhibitors*. US 2006035886, WO 2006020904.

2. Dyckman, A. et al. (Bristol-Myers Squibb Co.) *Pyrrolo-triazine aniline compounds useful as kinase inhibitors*. CA 2483164, EP 1497019, JP 2010132673, US 2004082582, US 7160883, WO 2003090912.

3. Kim, S. et al. (Bristol-Myers Squibb Co.) *Process for preparing salts of 4-[[5-[(cyclopropylamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide and novel stable forms produced therein*. US 2009312331.

4. Ji, P. et al. *Multiple-dose safety, tolerability, pharmacokinetics, and pharmacodynamics of a potent P38 inhibitor BMS-582949 in healthy subjects*. 72nd Annu Sci Meet Am Coll Rheumatol (Oct 24-29, San Francisco) 2008, Abst 355.

5. Kaul, S. et al. *Anti-inflammatory effects of BMS-582949, a P38 mitogen activated protein kinase (MAPK) inhibitor, during experimental endotoxemia in healthy male subjects*. 72nd Annu Sci Meet Am Coll Rheumatol (Oct 24-29, San Francisco) 2008, Abst 354.

6. Liu, C. et al. *Discovery of 4-(5-(Cyclopropylcarbamoyl)-2-methylphenylamino)-5-methyl-N-propylpyrrolo[1,2-f][1,2,4]triazine-6-carboxamide (BMS-582949), a clinical p38a MAP kinase inhibitor for the treatment of inflammatory diseases*. J Med Chem 2010, 53(18): 6629.

7. Liu, C. et al. *Discovery of BMS-582949, a clinical p38a MAP kinase inhibitor for the treatment of inflammatory diseases*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 290.

8. Wang, J. et al. *Multiple ascending dose study of a potent p38 MAPK inhibitor BMS-582949 in subjects with stable RA receiving concomitant methotrexate*. 72nd Annu Sci Meet Am Coll Rheumatol (Oct 24-29, San Francisco) 2008, Abst 356.

9. *A phase IIa study of BMS-582949 in patients with moderate to severe plaque psoriasis (NCT00399906)*. ClinicalTrials.gov Web Site 2007, Jan 16.

10. *Bristol-Myers begins phase II trial of p38 kinase inhibitor BMS-582949 for psoriasis*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2007, Sept 20.

11. *Efficacy study of p38 kinase inhibitor to treat patients with atherosclerosis (NCT00570752)*. ClinicalTrials.gov Web Site 2007, Dec 21.

12. *Multiple ascending dose study of BMS-582949 in patients with stable rheumatoid arthritis on the methotrexate background (NCT00162292)*. ClinicalTrials.gov Web Site 2006, Nov 30.

13. *Phase 2 clinical studies initiated for a novel therapeutic candidate identified through Pharmacopeia collaboration*. Pharmacopeia Press Release 2007, Sept 18.

14. *PoC in rheumatoid arthritis with methotrexate (NCT00605735)*. ClinicalTrials.gov Web Site 2008, March 26.

LSC-1

699896

Recombinant fusion protein comprising three copies of an E-selectin-binding peptide, the translocation domain of Pseudomonas exotoxin A (ETA II) and the NEMO-binding peptide (NF-κB-inhibiting effector domain)

LSC1

ACTION – Nuclear factor NF-κB inhibitor that blocked the activation of NF-κB in E-selectin-expressing and wild-type CHO cells (MIC = 500 nM) and inhibited leukocyte interaction with endothelial cells (125-500 nM). Compound significantly reduced joint swelling in the acute and flare-up phase of methylated bovine serum-induced arthritis, experimental arthritis caused by K/BxN serum transfer in mice, cartilage, bone degradation and synovial inflammation. Potentially useful for the treatment of inflammatory joint diseases.

SOURCES – Friedrich-Alexander-Universität, Erlangen (DE); Johann Wolfgang Goethe Universität, Frankfurt (DE); Technische Universität Carolo-Wilhelmina zu Braunschweig, Braunschweig (DE); Westfälische Wilhelms-Universität Münster, Münster (DE).

REFERENCES

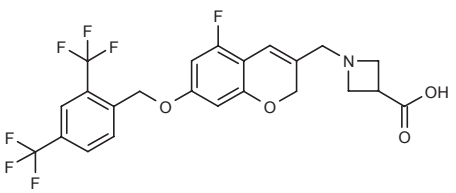
1. Sehnert, B. et al. *A tissue-specific NF-κB inhibitor: New prospects in the treatment of inflammatory joint diseases*. Annu Eur Congr Rheumatol (EULAR) (June 16-19, Rome) 2010, Abst OP0125.

2. Sehnert, B. et al. *A tissue-specific NF-κB inhibitor ameliorates inflammatory joint diseases*. Ann Rheum Dis 2010, 69 129635e.

IMMUNOMODULATING AGENTS

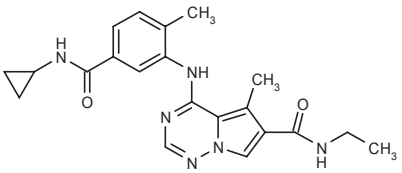
700769

1-[7-[2,4-Bis(trifluoromethyl)benzyloxy]-5-fluoro-2*H*-1-benzopyran-3-ylmethyl]azetidine-3-carboxylic acid



C23H18F7NO4; Mol wt: 505.3821

ACTION – Lysophospholipid S1P1 receptor agonist with an EC_{50} of 2 nM in [^{35}S]-GTPγS binding assays using human receptors expressed in CHO cells. In vivo it gave an ED_{50} value of 0.010 mg/kg p.o. at 4 h for blood lymphocyte depletion in male Lewis rats. Reported to be useful for the treatment of transplant rejection, autoimmune diseases, graft versus host disease, cancer and inflammation. Related compounds include:



BMS-573298 [706405][2,6,7]: C21H24N6O2

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REFERENCES

1. Cann, R.O. et al. (Bristol-Myers Squibb Co.) *Process for preparing pyrrolotriazine aniline compounds useful as kinase inhibitors*. US 2006035886, WO 2006020904.

2. Dyckman, A. et al. (Bristol-Myers Squibb Co.) *Pyrrolo-triazine aniline compounds useful as kinase inhibitors*. CA 2483164, EP 1497019, JP 2010132673, US 2004082582, US 7160883, WO 2003090912.

3. Kim, S. et al. (Bristol-Myers Squibb Co.) *Process for preparing salts of 4-[[5-[(cyclopropylamino)carbonyl]-2-methylphenyl]amino]-5-methyl-N-propylpyrrolo[2,1-f][1,2,4]triazine-6-carboxamide and novel stable forms produced therein*. US 2009312331.

4. Ji, P. et al. *Multiple-dose safety, tolerability, pharmacokinetics, and pharmacodynamics of a potent P38 inhibitor BMS-582949 in healthy subjects*. 72nd Annu Sci Meet Am Coll Rheumatol (Oct 24-29, San Francisco) 2008, Abst 355.

5. Kaul, S. et al. *Anti-inflammatory effects of BMS-582949, a P38 mitogen activated protein kinase (MAPK) inhibitor, during experimental endotoxemia in healthy male subjects*. 72nd Annu Sci Meet Am Coll Rheumatol (Oct 24-29, San Francisco) 2008, Abst 354.

6. Liu, C. et al. *Discovery of 4-(5-(Cyclopropylcarbamoyl)-2-methylphenylamino)-5-methyl-N-propylpyrrolo[1,2-f][1,2,4]triazine-6-carboxamide (BMS-582949), a clinical p38a MAP kinase inhibitor for the treatment of inflammatory diseases*. J Med Chem 2010, 53(18): 6629.

7. Liu, C. et al. *Discovery of BMS-582949, a clinical p38a MAP kinase inhibitor for the treatment of inflammatory diseases*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 290.

8. Wang, J. et al. *Multiple ascending dose study of a potent p38 MAPK inhibitor BMS-582949 in subjects with stable RA receiving concomitant methotrexate*. 72nd Annu Sci Meet Am Coll Rheumatol (Oct 24-29, San Francisco) 2008, Abst 356.

9. *A phase IIa study of BMS-582949 in patients with moderate to severe plaque psoriasis (NCT00399906)*. ClinicalTrials.gov Web Site 2007, Jan 16.

10. *Bristol-Myers begins phase II trial of p38 kinase inhibitor BMS-582949 for psoriasis*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2007, Sept 20.

11. *Efficacy study of p38 kinase inhibitor to treat patients with atherosclerosis (NCT00570752)*. ClinicalTrials.gov Web Site 2007, Dec 21.

12. *Multiple ascending dose study of BMS-582949 in patients with stable rheumatoid arthritis on the methotrexate background (NCT00162292)*. ClinicalTrials.gov Web Site 2006, Nov 30.

13. *Phase 2 clinical studies initiated for a novel therapeutic candidate identified through Pharmacopeia collaboration*. Pharmacopeia Press Release 2007, Sept 18.

14. *PoC in rheumatoid arthritis with methotrexate (NCT00605735)*. ClinicalTrials.gov Web Site 2008, March 26.

LSC-1

699896

Recombinant fusion protein comprising three copies of an E-selectin-binding peptide, the translocation domain of Pseudomonas exotoxin A (ETA II) and the NEMO-binding peptide (NF-κB-inhibiting effector domain)

LSC1

ACTION – Nuclear factor NF-κB inhibitor that blocked the activation of NF-κB in E-selectin-expressing and wild-type CHO cells (MIC = 500 nM) and inhibited leukocyte interaction with endothelial cells (125-500 nM). Compound significantly reduced joint swelling in the acute and flare-up phase of methylated bovine serum-induced arthritis, experimental arthritis caused by K/BxN serum transfer in mice, cartilage, bone degradation and synovial inflammation. Potentially useful for the treatment of inflammatory joint diseases.

SOURCES – Friedrich-Alexander-Universität, Erlangen (DE); Johann Wolfgang Goethe Universität, Frankfurt (DE); Technische Universität Carolo-Wilhelmina zu Braunschweig, Braunschweig (DE); Westfälische Wilhelms-Universität Münster, Münster (DE).

REFERENCES

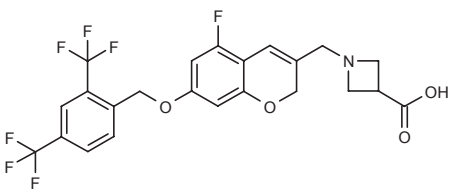
1. Sehnert, B. et al. *A tissue-specific NF-κB inhibitor: New prospects in the treatment of inflammatory joint diseases*. Annu Eur Congr Rheumatol (EULAR) (June 16-19, Rome) 2010, Abst OP0125.

2. Sehnert, B. et al. *A tissue-specific NF-κB inhibitor ameliorates inflammatory joint diseases*. Ann Rheum Dis 2010, 69 129635e.

IMMUNOMODULATING AGENTS

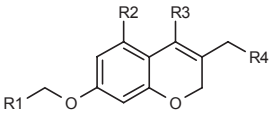
700769

1-[7-[2,4-Bis(trifluoromethyl)benzyloxy]-5-fluoro-2*H*-1-benzopyran-3-ylmethyl]azetidine-3-carboxylic acid



C23H18F7NO4; Mol wt: 505.3821

ACTION – Lysophospholipid S1P1 receptor agonist with an EC_{50} of 2 nM in [^{35}S]-GTPγS binding assays using human receptors expressed in CHO cells. In vivo it gave an ED_{50} value of 0.010 mg/kg p.o. at 4 h for blood lymphocyte depletion in male Lewis rats. Reported to be useful for the treatment of transplant rejection, autoimmune diseases, graft versus host disease, cancer and inflammation. Related compounds include:



Compound	R1	R2	R3	R4	Formula
700776	2-MeO-4-Pr-Ph	H	H	3-CO2H-1-azetidinyl	$C_{25}H_{29}NO_5$
700777	2,4-(CF3)2-Ph	H	Cl	3-CO2H-1-azetidinyl	$C_{23}H_{18}ClF_6NO_4$
700780	2-MeO-4-Pr-Ph	H	H	3-CO2H-1-pyrrolidinyl	$C_{26}H_{31}NO_5$
700785	5-Et-4-Ph-2-thienyl	F	H	3-CO2H-1-pyrrolidinyl	$C_{28}H_{28}FNO_4S$
700791	5-CF3-4-Ph-2-thienyl	F	H	3-CO2H-4-Me--1-pyrrolidinyl	$C_{28}H_{25}F_4NO_4S$
700797	3-CF3-4-[(S)-CF3CH(Me)O]-Ph	F	H	3-CO2H-1,2,5,6--tetrahydro-1-Pyr	$C_{27}H_{24}F_7NO_5$
700798	3-CF3-4-[CH(CH2F)2O]-Ph	F	H	3(S)-CO2H-1-Pip	$C_{27}H_{27}F_6NO_5$

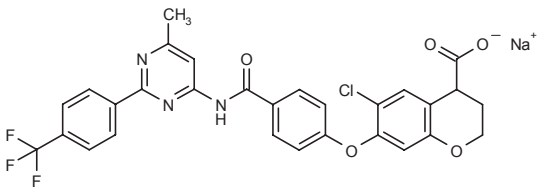
SOURCE – Astellas Pharma.

REFERENCES

1. Harada, H. et al. (Astellas Pharma Inc.) *2H-Chromene compound and derivative thereof*. WO 2010064707.

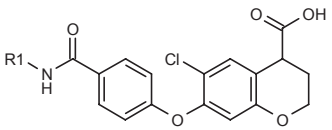
701330

6-Chloro-7-[4-[*N*-[6-methyl-2-[4-(trifluoromethyl)phenyl]pyrimidin-4-yl]carbamoyl]phenoxy]-3,4-dihydro-*2H*-1-benzopyran-4-carboxylic acid sodium salt



C29H20ClF3N3NaO5; Mol wt: 605.9240

ACTION – Prostanoid DP2 receptor antagonist that suppressed the binding of [^{3}H]-PGD_2 to the human DP2 expressed in human leukemia K-562 cells with an EC_{50} of 21.2 nM. Reported to be useful for the treatment of immunological disorders, as well as allergic disorders such as asthma, allergic rhinitis, atopic dermatitis and other inflammatory disorders. Related compounds include:



Compound	R1	Formula
701321	6-(4-Cl-Ph)-2-Pyr	$C_{28}H_{20}Cl_2N_2O_5$
701326	1-[3,4-(Cl)2-Ph]-3-pyrazolyl	$C_{26}H_{18}Cl_3N_3O_5$
701328	6-(4-CF3-Ph)-2-Pyr	$C_{29}H_{20}ClF_3N_2O_5$

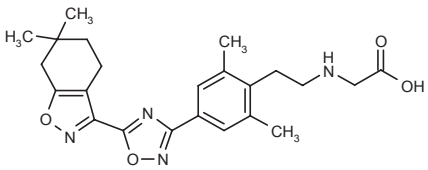
SOURCE – Array BioPharma.

REFERENCES

1. Cook, A. et al. (Array BioPharma, Inc.) *7-Phenoxychroman carboxylic acid derivatives*. WO 2010075200.

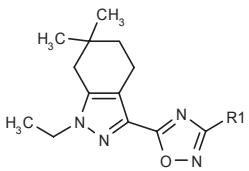
701560

N-[2-[4-[5-(6,6-Dimethyl-4,5,6,7-tetrahydrobenzisoxazol-3-yl)-1,2,4-oxadiazol-3-yl]-2,6-dimethylphenyl]ethyl]glycine



C23H28N4O4; Mol wt: 424.4928

ACTION – Lysophospholipid S1P1 receptor agonist with an EC_{50} of 1.7 nM in [^{35}S]-GTPγS binding assays. Reported to be useful for the treatment of transplant rejection, multiple sclerosis, systemic lupus erythematosus, asthma, psoriasis, rheumatoid arthritis, psoriatic arthritis and Crohn's disease. Further applications include malignant neoplasms, angiogenesis-related disorders, pain, neurological disorders, viral and infectious diseases. Related compounds include:



Compound	R1	Formula
701571	2-(CO2HCH2NH)-1,2,3,4-tetrahydro-6-Naph	$C_{25}H_{31}N_5O_3$
701580	4-(NH2CH2CH2)-2-Me-Ph	$C_{22}H_{29}N_5O$

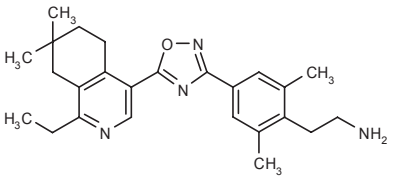
SOURCE – Almirall.

REFERENCES

1. Giulio Matassa, V. et al. (Laboratorios Almirall, SA) *1,2,4-Oxadiazole derivatives and their therapeutic use*. EP 2202232, WO 2010072352.

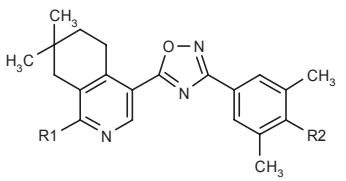
704231

2-[4-[5-(1-Ethyl-7,7-dimethyl-5,6,7,8-tetrahydroisoquinolin-4-yl)-1,2,4-oxadiazol-3-yl]-2,6-dimethylphenyl]ethylamine



C25H32N4O; Mol wt: 404.5478

ACTION – Lysophospholipid S1P1 receptor agonist with an EC_{50} of 10.8 nM in [^{35}S]-GTPγS binding assays. Reported to be useful for the treatment of transplant rejection, multiple sclerosis, systemic lupus erythematosus, asthma, psoriasis, rheumatoid arthritis, psoriatic arthritis and Crohn's disease. Further applications include malignant neoplasms, angiogenesis-related disorders, pain, neurological disorders, viral and infectious diseases. Other representative compounds are:



Compound	R1	R2	Formula
704219	N(Me)2	CH2CH(OH)CH2OH	$C_{26}H_{34}N_4O_3$
704221	NHMe	OCH2CH2NH2	$C_{24}H_{31}N_5O_2$
704224	H	3-CO2H-1-azetidinyl-CH2CH2	$C_{27}H_{32}N_4O_3$
704226	H	CH2CH2NHCH2CHF2	$C_{25}H_{30}F_2N_4O$
704227	H	CH2CH(OH)CH2OH	$C_{24}H_{29}N_3O_3$
704229	cyclopropyl	CH2CH2CO2H	$C_{27}H_{31}N_3O_3$
704233	Et	CH2CH2CONH2	$C_{26}H_{32}N_4O_2$

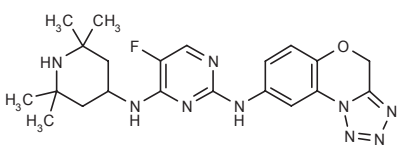
SOURCE – Almirall.

REFERENCES

1. Aguilar Izquierdo, N. et al. (Laboratorios Almirall, SA) *Oxadiazole derivatives as S1P1 receptor agonists*. EP 2210890, WO 2010081692.

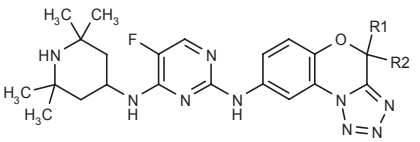
704319

5-Fluoro-*N*^{4}-(2,2,6,6-tetramethylpiperidin-4-yl)-*N*^{2}-(4*H*-tetrazolo-[5,1-*c*][1,4]benzoxazin-8-yl)pyrimidine-2,4-diamine

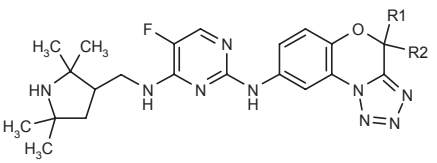


C21H26FN9O; Mol wt: 439.4892

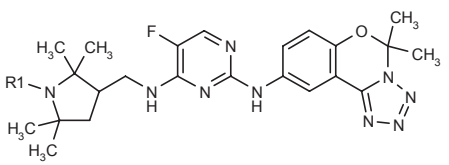
ACTION – Protein kinase PKC inhibitor that suppressed human recombinant PKC-α, -β1, -δ, -ε and -θ with an IC_{50} of < 0.25 μM and displayed an IC_{50} value < 0.25 μM in whole cell assays using human primary T cells. Reported to be useful for the treatment of autoimmune diseases including graft versus host disease, and inflammation, eye disorders involving inflammation and neovascularization, and cell proliferative disorders, among others. Other representative compounds are:



Compound	R1	R2	Formula
704323	Me	Me	$C_{23}H_{30}FN_9O$
704325	-(CH2)3-		$C_{24}H_{30}FN_9O$
704327	H	Me	$C_{22}H_{28}FN_9O$



Compound	R1=R2	Isomer	Formula
704331	H		$C_{21}H_{26}FN_9O$
704332	Me	(+), S	$C_{23}H_{30}FN_9O$



Compound	R1	Formula
704333	H	$C_{23}H_{30}FN_9O$
704334	Me	$C_{24}H_{32}FN_9O$

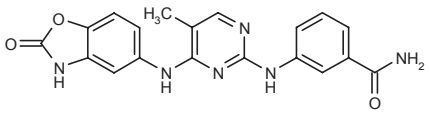
SOURCE – Rigel.

REFERENCES

1. Zhao, H. et al. (Rigel Pharmaceuticals, Inc.) *Protein kinase C inhibitors and uses thereof*. US 2010184755, WO 2010083207.

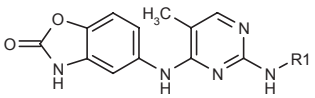
705466

3-[5-Methyl-4-(2-oxo-2,3-dihydrobenzoxazol-5-ylamino)pyrimidin-2-ylamino]benzamide

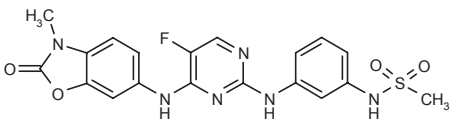


C19H16N6O3; Mol wt: 376.3687

ACTION – Tyrosine-protein kinase JAK3 inhibitor (IC_{50} < 0.5 μM) reported to be useful for in the treatment of transplant rejection, T-cell-mediated autoimmune diseases and eye disorders. Other representative compounds are:



Compound	R1	Formula
705469	4-(CO2Me)-Ph	$C_{20}H_{17}N_5O_4$
705470	3-F-5-Me-Ph	$C_{19}H_{16}FN_5O_2$
705471	3-Br-Ph	$C_{18}H_{14}BrN_5O_2$
705472	3-[4-(CO2Et)-1-Piz]-Ph	$C_{25}H_{27}N_7O_4$
705473	6-(4-Me-1-Piz)-3-Pyr	$C_{22}H_{24}N_8O_2$
705474	6-(MeOCH2CH2O)-3-Pyr	$C_{20}H_{20}N_6O_4$



705467: C19H17FN6O4S

SOURCE – Rigel.

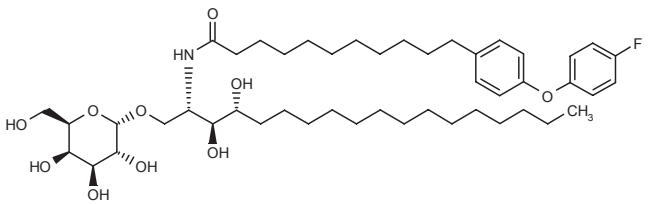
REFERENCES

1. Li, H. et al. (Rigel Pharmaceuticals, Inc.) *Compositions and methods for inhibition of the JAK pathway*. US 2010190770, WO 2010085684.

C-34

686336

11-[4-(4-Fluorophenoxy)phenyl]-*N*-[1-(α-D-galactopyranosyloxy)-3(*S*),4(*R*)-dihydroxyoctadecan-2(*S*)-yl]undecanamide



C47H76FNO10; Mol wt: 834.1054

ACTION – α-Galactosyl ceramide analogue that binds to CD1d on dendritic cells and activates invariant natural killer T cells to secrete Th1 and Th2 cytokines. Compound displayed antibacterial activity in mice infected with *Sphingomonas capsulata* and *Staphylococcus aureus* at 50 or 100 and 150 μg/kg i.p., respectively, and protected against Japanese encephalitis virus and influenza virus A (WSN) infections in mice at 1 μg/kg i.p. Compound was more effective when administered as prophylaxis before or shortly after infection. Potentially useful as immunotherapy and treatment of infections and cancer.

SOURCE – Academia Sinica, Taipei (TW).

REFERENCES

1. Wong, C.-H. et al. (Academia Sinica) *alpha-Galactosyl ceramide analogs and their use as immunotherapies, adjuvants, and antiviral, antibacterial, and anticancer agents*. US 2010008954, WO 2010006315.

2. Wong, C.-H. et al. (Academia Sinica) *Globo H and related anti-cancer vaccines with novel glycolipid adjuvants*. US 2010136042, WO 2010005598.

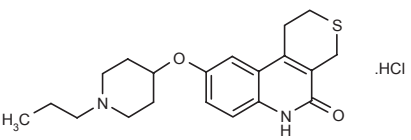
3. Lin, K.-H. et al. *In vivo protection of bacterial and viral infections in murine models using a synthetic new alpha-GalCer analog* . Antimicrob Agents Chemother 2010, 54(10): 4129.

TREATMENT OF CANCER

CANCER CHEMOTHERAPY

680049

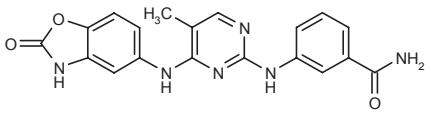
9-(1-Propylpiperidin-4-yloxy)-2,4,5,6-tetrahydro-1*H*-thiopyrano-[3,4-*c*]quinolin-5-one hydrochloride



C20H27ClN2O2S; Mol wt: 394.9590

705466

3-[5-Methyl-4-(2-oxo-2,3-dihydrobenzoxazol-5-ylamino)pyrimidin-2-ylamino]benzamide



C19H16N6O3; Mol wt: 376.3687

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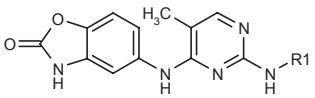

Compound	R1	Formula
705469	4-(CO2Me)-Ph	$C_{20}H_{17}N_5O_4$
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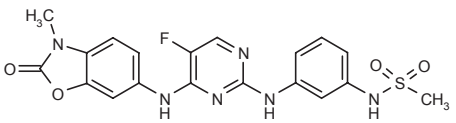
705471	3-Br-Ph	$C_{18}H_{14}BrN_5O_2$
705472	3-[4-(CO2Et)-1-Piz]-Ph	$C_{25}H_{27}N_7O_4$
705473	6-(4-Me-1-Piz)-3-Pyr	$C_{22}H_{24}N_8O_2$
705474	6-(MeOCH2CH2O)-3-Pyr	$C_{20}H_{20}N_6O_4$



705467: C19H17FN6O4S

SOURCE – Rigel.

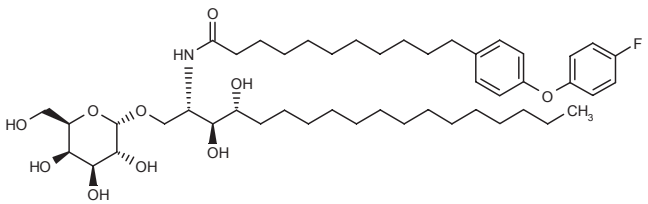
REFERENCES

1. Li, H. et al. (Rigel Pharmaceuticals, Inc.) *Compositions and methods for inhibition of the JAK pathway*. US 2010190770, WO 2010085684.

C-34

686336

11-[4-(4-Fluorophenoxy)phenyl]-*N*-[1-(α-D-galactopyranosyloxy)-3(*S*),4(*R*)-dihydroxyoctadecan-2(*S*)-yl]undecanamide



C47H76FNO10; Mol wt: 834.1054

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REFERENCES

1. Wong, C.-H. et al. (Academia Sinica) *alpha-Galactosyl ceramide analogs and their use as immunotherapies, adjuvants, and antiviral, antibacterial, and anticancer agents*. US 2010008954, WO 2010006315.

2. Wong, C.-H. et al. (Academia Sinica) *Globo H and related anti-cancer vaccines with novel glycolipid adjuvants*. US 2010136042, WO 2010005598.

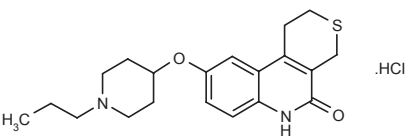
3. Lin, K.-H. et al. *In vivo protection of bacterial and viral infections in murine models using a synthetic new alpha-GalCer analog* . Antimicrob Agents Chemother 2010, 54(10): 4129.

TREATMENT OF CANCER

CANCER CHEMOTHERAPY

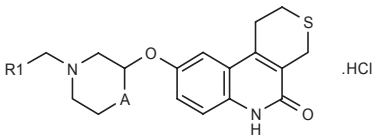
680049

9-(1-Propylpiperidin-4-yloxy)-2,4,5,6-tetrahydro-1*H*-thiopyrano-[3,4-*c*]quinolin-5-one hydrochloride



C20H27ClN2O2S; Mol wt: 394.9590

ACTION – Poly(ADP-ribose)polymerase PARP-1 inhibitor (IC_{50} = 0.042 and 0.22 μM, respectively, in enzymatic and cellular assays), reported to be useful for the treatment of cancer, ischemic stroke, epilepsy, osteoarthritis, neurological diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cardiovascular diseases such as atherosclerosis, myocardial infarction and angina pectoris, neuropathic pain, osteoporosis and schizophrenia. Other related compounds include:



Compound	R1	A	Formula
661085	H	CH2	$C_{18}H_{23}ClN_2O_2S$
661089	Me	CH2	$C_{19}H_{25}ClN_2O_2S$
695097	Me	bond	$C_{18}H_{23}ClN_2O_2S$

SOURCE – Jeil Pharmaceutical.

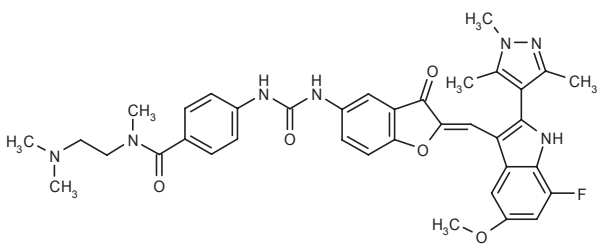
REFERENCES

1. Choi, J.-H. et al. (Jeil Pharmaceutical Co. Ltd.) *Novel tricyclic derivatives or pharmaceutically acceptable salts thereof, process for the preparation thereof and pharmaceutical composition comprising the same*. WO 2009061131.

2. Park, C.H. et al. *Synthesis and evaluation of tricyclic derivatives containing a non-aromatic amide as inhibitors of poly(ADP-ribose)polymerase-1 (PARP-1)*. Bioorg Med Chem Lett 2010, 20(7): 2250.

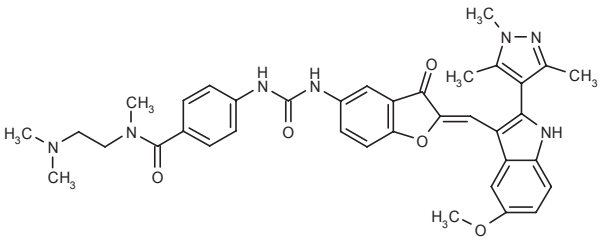
683867*

N-[2-(Dimethylamino)ethyl]-4-[3-[2(*Z*)-[7-fluoro-5-methoxy-2-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-1*H*-indol-3-ylmethylidene]-3-oxo-2,3-dihydro-1-benzofuran-5-yl]ureido]-*N*-methylbenzamide



C37H38FN7O5; Mol wt: 679.7399

ACTION – Phosphatidylinositol 3-kinase (PI3K) Inhibitor (IC_{50} = 0.20, 0.7, 2.4, 0.6 and 0.3 nM, respectively, for PI3Kα, β, γ and δ and mTOR) that inhibited the proliferation of human breast carcinoma MDA-MB-361 and human prostate carcinoma PC-3 cells (IC_{50} < 3 and 10 nM, respectively). Compound 25 mg/kg i.v. on days 1, 5 and 9 was able to shrink tumor size in mice bearing MDA-MB-361 xenografts. Reported to be useful for the treatment of cancer, restenosis, atherosclerosis, bone disorders, psoriasis, inflammation, angiogenesis, benign prostatic hypertrophy, immunological and renal disorders. Another representative compound is:



683871:** C37H39N7O5

SOURCE – Pfizer.

REFERENCES

1. Bursavich, M.G. et al. (Wyeth) *3-Substituted-1H-indole compounds, their use as mTOR kinase and PI3 kinase inhibitors, and their syntheses*. US 2009311217, WO 2009155042.

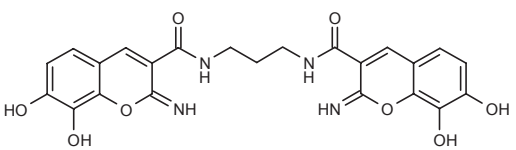
2. Zhang, N. et al. *5-ureidobenzofuranone indoles as potent and efficacious inhibitors of PI3 kinase-alpha and mTOR for the treatment of breast cancer*. Bioorg Med Chem Lett 2010, 20(12): 3526.

*Identified compound **683867** Drug Data Rep 2010, 032(01): 0096.

Identified compound **683871 (see **683867**) Drug Data Rep 2010, 032(01): 0096.

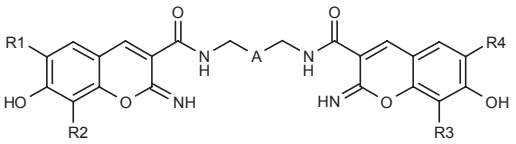
698429

N,*N*'-(Propane-1,3-diyl)bis(7,8-dihydroxy-2-imino-2*H*-1-benzopyran-3-carboxamide)



C23H20N4O8; Mol wt: 480.4269

ACTION – Dynamin GTPase I and II inhibitor (IC_{50} = 450 and 390 nM, respectively) that blocked receptor-mediated endocytosis in human bone osteosarcoma U-2 OS cells (IC_{50} = 10 μM) and synaptic vesicle endocytosis (IC_{50} = 99 μM). Reported to be useful for the treatment of cancer and pathogenic infections. Other related compounds are:



Compound	R1=R4	R2=R3	A	Formula
698427	H	OH	bond	$C_{22}H_{18}N_4O_8$
698428	OH	H	CH2	$C_{23}H_{20}N_4O_8$

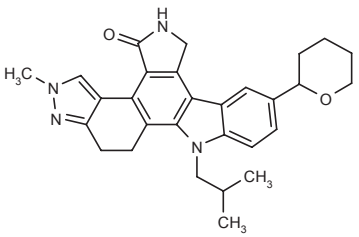
SOURCES – University of Newcastle, Australia, Newcastle (AU); University of Sydney, Sydney (AU).

REFERENCES

1. Hill, T.A. et al. *Iminochromene inhibitors of dynamins I and II GTPase activity and endocytosis*. J Med Chem 2010, 53(10): 4094.

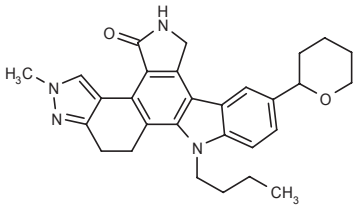
698910

11-Isobutyl-2-methyl-8-(tetrahydropyran-2-yl)-4,5,6,11,12,13-hexahydro-2*H*-indazolo[5,4-*a*]pyrrolo[3,4-*c*]carbazol-4-one



C29H32N4O2; Mol wt: 468.5900

ACTION – Dual tyrosine-protein kinase receptor TIE-2/vascular endothelial growth factor receptor VEGFR-2 inhibitor that showed IC_{50} values of 3 and 11 nM, respectively, against TIE-2 and VEGFR-2 in biochemical assays and exhibited selectivity over other serine/threonine kinases; it also suppressed VEGF-induced VEGFR-2 phosphorylation (IC_{50} = 10-50 nM) and angiogenesis (EC_{50} = 0.9 nM) in human umbilical vein enthothelial cells (HUVECs). Compound reduced the viability of HUVECs with an EC_{50} of 2 nM and it significantly inhibited tumor growth at 1 mg/kg p.o. b.i.d. for 10 days in mice bearing angiosarcoma SVR xenografts. Potentially useful for the treatment of angiogenesis and cancer. Another representative compound is:



698912: C29H32N4O2

SOURCE – Cephalon.

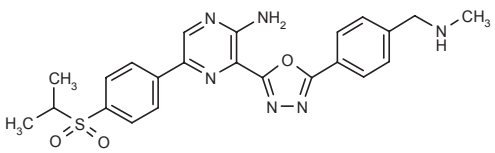
REFERENCES

1. Becknell, N.C. et al. (Cephalon, Inc.) *Novel fused pyrrolocarbazoles*. EP 1704148, JP 2007516293, US 2005143442, US 7169802, WO 2005063763.

2. Hudkins, R.L. et al. *8-THP-DHI analogs as potent Type I dual TIE-2/VEGF-R2 receptor tyrosine kinase inhibitors*. Bioorg Med Chem Lett 2010, 20(11): 3356.

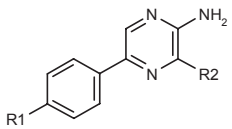
700680

5-[4-(Isopropylsulfonyl)phenyl]-3-[5-[4-(methylaminomethyl)phenyl]-1,3,4-oxadiazol-2-yl]pyrazin-2-amine



C23H24N6O3S; Mol wt: 464.5400

ACTION – Serine/threonine-protein kinase ATR inhibitor (K_i < 100 nM in an enzymatic assay; IC_{50} < 100 nM in a cellular assay) that displayed antiproliferative activity against human colorectal HCT 116 cells cancer cell lines (IC_{50} = 100 nM-1 µM) and was able to sensitize HCT 116 cells to cisplatin (IC_{50} < 100 nM). Reported to be useful for the treatment of cancer. Related compounds include:



Compound	R1	R2	Formula
700676	SO2Me	CONHPh	$C_{18}H_{16}N_4O_3S$
700677	1-Piz-CO	2-benzimidazolyl	$C_{22}H_{21}N_7O$
700678	i-PrSO2	3-[4-[HOCH(Me)CH2NHCH2]-Ph]-5-isoxazolyl	$C_{26}H_{29}N_5O_4S$

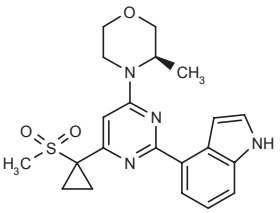
SOURCE – Vertex.

REFERENCES

1. Charrier, J.-D. et al. (Vertex Pharmaceuticals Inc.) *Pyrazine derivatives useful as inhibitors of ATR kinase*. WO 2010071837.

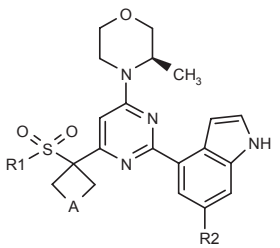
701166

4-[4-[3(*R*)-Methylmorpholin-4-yl]-6-[1-(methylsulfonyl)cyclopropyl]pyrimidin-2-yl]-1*H*-indole



C21H24N4O3S; Mol wt: 412.5050

ACTION – Serine/threonine-protein kinase ATR inhibitor (average IC_{50} = 0.003973 µM) that also inhibited serine/threonine-protein kinase mTOR (IC_{50} = 0.02673 µM). Compound potentiated the effects of carboplatin 0.3 and 0.1 µM against human colon adenocarcinoma HT-29 cells with IC_{50} values of 0.39 and 1.96 µg/mL, respectively Related compounds include:



Compound	R1	R2	A	Formula
701167	Me	OMe	-CH2OCH2-	$C_{24}H_{30}N_4O_5S$
701170	Me	H	-CH2-	$C_{22}H_{26}N_4O_3S$
701173	cyclopropyl	H	bond	$C_{23}H_{26}N_4O_3S$
701175	Et	H	bond	$C_{22}H_{26}N_4O_3S$
701176	i-Pr	H	bond	$C_{23}H_{28}N_4O_3S$

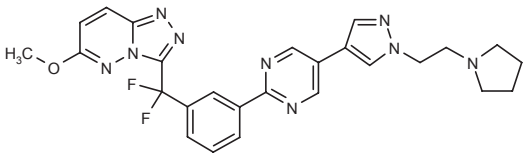
SOURCE – AstraZeneca.

REFERENCES

1. Foote, K.M. and Nissink, J.W.M. (AstraZeneca plc;AstraZeneca AB) *Pyrimidine indole derivatives for treating cancer*. WO 2010073034.

701178

3-[1,1-Difluoro-1-[3-[5-[1-[2-(1-pyrrolidinyl)ethyl]-1*H*-pyrazol-4-yl]pyrimidin-2-yl]phenyl]methyl]-6-methoxy[1,2,4]triazolo[4,3-*b*]-pyridazine



C26H25F2N9O; Mol wt: 517.5332

ACTION – Proto-oncogene c-Met inhibitor (IC_{50} = 1 nM-0.1 µM in enzymatic and cellular assays), potentially useful for the treatment of cancer.

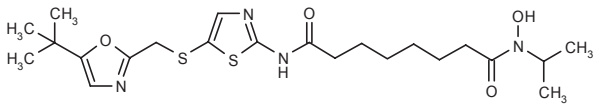
SOURCE – Merck KGaA.

REFERENCES

1. Dorsch, D. et al. (Merck Patent GmbH) *3-(3-Pyrimidine-2-yl-benzyl)-[1,2,4]triazolo[4,3-b]pyridazine derivatives*. DE 102008062825, WO 2010072301.

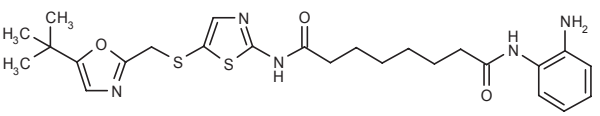
701312

N^1-[5-(5-*tert*-Butyloxazol-2-ylmethylsulfanyl)thiazol-2-yl]-N^8-hydroxy-N^8-isopropyloctanediamide



C22H34N4O4S2; Mol wt: 482.6600

ACTION – Cyclin-dependent kinase inhibitor that suppressed the activities of CDK1, CDK2, CDK3 and CDK9 with IC_{50} values of ≤ 0.1 µM and the activity of CDK4 with an IC_{50} of 0.1-1 µM. Reported to be useful for the treatment of cancer, as well as viral infections such as HIV, human papillomavirus, herpesvirus, poxvirus, Epstein-Barr virus, sindbis virus and adenovirus infections. A related compound is:



701311: C25H33N5O3S2

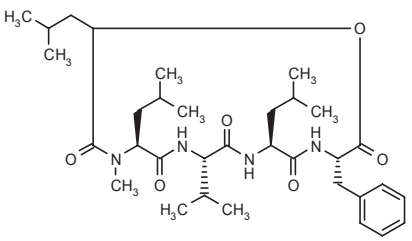
SOURCE – Curis.

REFERENCES

1. Qian, C. et al. (Curis, Inc.) *CDK inhibitors*. WO 2010075542.

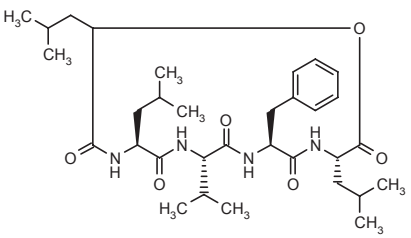
701853

N-(2-Hydroxy-4-methylpentanoyl)-*N*-methyl-L-leucyl-L-valyl-L-leucyl-L-phenylalanine *C*-1.5-*O*-2.1-lactone



C33H52N4O6; Mol wt: 600.7892

ACTION – Cyclic pentadepsipeptide isolated from *Fusarium solani* KCCM90040 that displayed cytotoxicity against human lung carcinoma A549, ovarian adenocarcinoma SK-OV-3 and SK-MEL-2, uterine sarcoma MEA-SA, colorectal adenocarcinoma HCT-15 and multidrug-resistant MES-SA/DX5 and HCT-15/CL02 cells, with EC_{50} values of 10.73, 11.24, 10.02, 13.96, 12.46, 11.42 and 13.50 μM, respectively. It significantly enhanced the cytotoxic activity of paclitaxel (3 μM) against HCT-15, MES-SA/DX5 and HCT-15/CL02 cells, with EC_{50} values of 0.1, 1.58 and 288.40 nM, respectively. Another exemplified compound is:



701857: C32H50N4O6

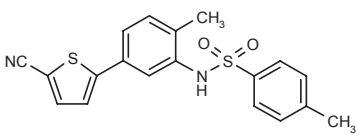
SOURCE – Chung-Ang University, Seoul, (KR).

REFERENCES

1. Lee, C. et al. (Chung-Ang University) *Cyclic penta-depsipeptide and Fusarium sp. microorganism producing the same*. WO 2010076905.

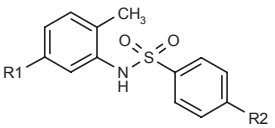
701893

N-[5-(5-Cyanothien-2-yl)-2-methylphenyl]-4-methylbenzenesulfonamide



C19H16N2O2S2; Mol wt: 368.4730

ACTION – Hypoxia-inducible factor HIF-1α inhibitor that suppressed estrogen receptor-mediated transcriptional activity in a transfection assay using human breast adenocarcinoma MCF7 cells (IC_{50} < 500 nM) and activated caspase-3/7 response in multiple myeloma HG-1 cells (EC_{50} < 500 nM). Compound also induced apoptosis in human leukemia HL-60 cells and displayed antiproliferative activity against MCF7 and HG-1 cells (EC_{50} < 500 nM). Potentially useful for the treatment of cancer and other hyperproliferative disorders, as well as inflammation. Related compounds include:



Compound	R1	R2	Formula
701888	4-CN-Ph	OMe	$C_{21}H_{18}N_2O_3S$
701889	4-CN-Ph	Me	$C_{21}H_{18}N_2O_2S$
701890	4-CN-2-thienyl	OMe	$C_{19}H_{16}N_2O_3S_2$
701891	5-CN-2-thienyl	OMe	$C_{19}H_{16}N_2O_3S_2$

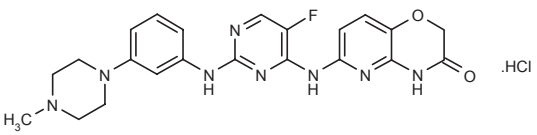
SOURCES – Elara Pharmaceuticals; European Molecular Biology Laboratory.

REFERENCES

1. Alonso, J. et al. (European Molecular Biology Laboratory;Elara Pharmaceuticals GmbH) *Toluidine sulfonamides and their use*. WO 2010075869, WO 2010076033.

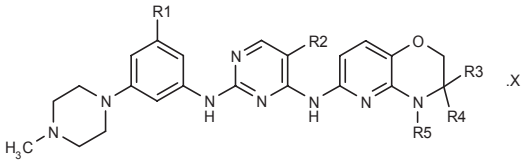
702127

6-[5-Fluoro-2-[3-(4-methylpiperazin-1-yl)phenylamino]pyrimidin-4-ylamino]-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-3-one hydrochloride

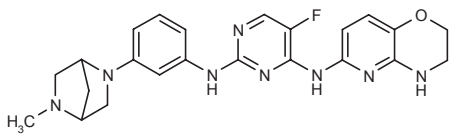


C22H24ClFN8O2; Mol wt: 486.9300

ACTION – Serine/threonine-protein kinase PLK1 inhibitor that suppressed PLK1 expressed in human chronic myelogenous leukemia K-562 cells with an IC_{50} of < 0.5 μM in both cellular and biochemical assays. Described as useful for the treatment of cancer. Related compounds include:



Compound	R1	R2	R3	R4	R5	X	Formula
702128	i-PrO	F	H	H	H		$C_{25}H_{31}FN_8O_2$
702130	cyclopropyl	F	H	H	H		$C_{25}H_{29}FN_8O$
702132	H	Me	-O-		2-propynyl		$C_{26}H_{28}N_8O_2$
702134	H	F	-O-		CH(Et)2		$C_{27}H_{33}FN_8O_2$
702135	H	F	-O-		H		$C_{22}H_{23}FN_8O_2$
702140	H	F	H	H	H	HCl	$C_{22}H_{26}ClFN_8O$



702129: C23H25FN8O

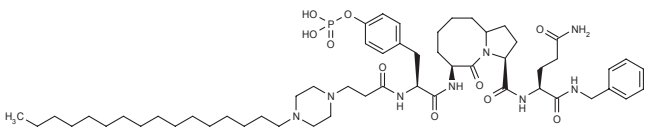
SOURCE – Rigel.

REFERENCES

1. Singh, R. et al. (Rigel Pharmaceuticals, Inc.) *Pyrimidinediamine kinase inhibitors*. US 2010179134, WO 2010078369.

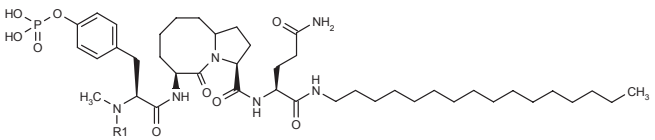
702143

N^1-Benzyl-*N*^{2}-[6(*S*)-[*N*-[3-(4-hexadecylpiperazin-1-yl)propionyl]-*O*-phosphono-L-tyrosinamido]-5-oxoperhydropyrrolo[1,2-*a*]azocin-3(*S*)-ylcarbonyl]-L-glutamamide

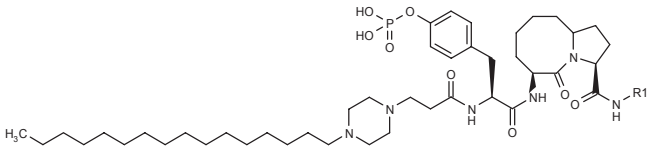


C55H87N8O10P; Mol wt: 1051.3006

ACTION – STAT3 inhibitor (IC_{50} < 1 µM in a binding assay that inhibited the growth of human breast adenocarcinoma MDA-MB-231 and MDA-MB-468 cells with IC_{50} values of < 10 µM. Related compounds include:



Compound	R1	Formula
702145	H	$C_{42}H_{71}N_6O_9P$
702147	Me	$C_{43}H_{73}N_6O_9P$



Compound	R1	Formula
702149	(CH2)3CH(OH)CH2OH	$C_{48}H_{83}N_6O_{10}P$
702150	5-imidazolyl-CH2CH2	$C_{48}H_{79}N_8O_8P$
702155	(S)-4-imidazolyl-CH2CH(CH2OH)	$C_{49}H_{81}N_8O_9P$
702157	4H-1,2,4-triazol-3-yl-CH2CH2	$C_{47}H_{78}N_9O_8P$
702158	4-pyrazolyl-CH2CH2	$C_{48}H_{79}N_8O_8P$

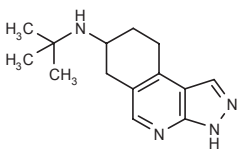
SOURCE – University of Michigan, Ann Arbor, MI (US).

REFERENCES

1. Wang, S. et al. (University of Michigan) *STAT3 inhibitors and therapeutic methods using the same*. WO 2010077589.

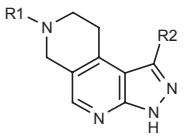
702378

N-tert-Butyl-6,7,8,9-tetrahydro-3*H*-pyrazolo[3,4-*c*]isoquinolin-7-amine

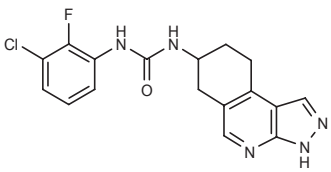


C14H20N4; Mol wt: 244.3354

ACTION – Fibroblast growth factor receptor FGFR2 inhibitor that suppressed the growth of human breast adenocarcinoma MDA-MB-231, colon adenocarcinoma DLD-1, gastric carcinoma KATO III, non-small cell carcinoma NCI-H1299 and pancreatic carcinoma MIA PaCa-2 cancer cells by 75-100% at 10 µM. Related compounds include:



Compound	R1	R2	Formula
702380	SO2Me	H	$C_{10}H_{12}N_4O_2S$
702381	4-N(Me)2-PhNHCO	H	$C_{18}H_{20}N_6O$
702383	2,4-(NH2)2-1,3,5-triazin-6-yl	H	$C_{12}H_{13}N_9$
702385	2-NH2-9H-purin-6-yl	H	$C_{14}H_{13}N_9$
702386	3-(4-morpholinyl--CH2CH2NHCO)-PhNHCO	H	$C_{23}H_{27}N_7O_3$
702387	CONHPh	3-CF3-Ph	$C_{23}H_{18}F_3N_5O$



702389: C17H15ClFN5O

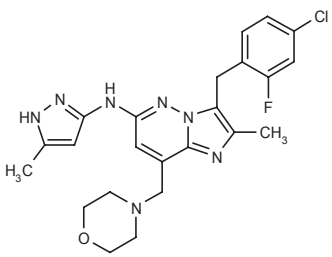
SOURCE – ArQule.

REFERENCES

1. Tandon, M. et al. (ArQule, Inc.) *Substituted pyrazolo[3,4-b]pyridine compounds*. WO 2010078427.

702513

3-(4-Chloro-2-fluorobenzyl)-2-methyl-*N*-(5-methyl-1*H*-pyrazol-3-yl)-8-(morpholin-4-ylmethyl)imidazo[1,2-*b*]pyridazin-6-amine



C23H25ClFN7O; Mol wt: 469.9420

ACTION – Tyrosine-protein kinase JAK2 inhibitor (IC_{50} = 0.033 μM) that showed selectivity over JAK3 inhibition (IC_{50} = 0.94 μM). It suppressed JAK2V617F expressed in Ba/F3 cells (IC_{50} = 0.03 μM). Reported to be useful for the treatment of cancer such as glioblastoma, breast cancer, multiple myeloma, prostate cancer and leukemia, and myeloproliferative disorders such as polycythemia vera, essential thrombocytosis and myelosclerosis with myeloid metaplasia.

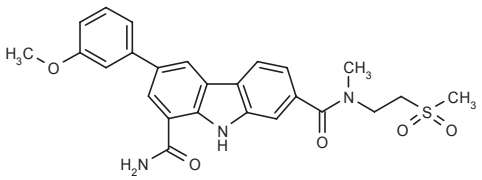
SOURCE – Lilly.

REFERENCES

1. Burkholder, T.P. et al. (Eli Lilly and Company) *Amino pyrazole compound*. US 2010152181, WO 2010074947.

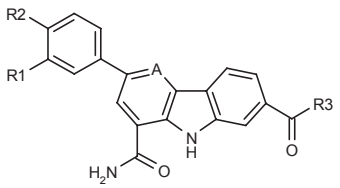
702748

3-(3-Methoxyphenyl)-*N*^{7}-methyl-N7-[2-(methylsulfonyl)ethyl]-9*H*-carbazole-1,7-dicarboxamide



C25H25N3O5S; Mol wt: 479.5480

ACTION – Tyrosine-protein kinase JAK2 inhibitor (IC_{50} < 0.001 μM) reported to be useful for the treatment of multiple myeloma and myeloproliferative disorders such as polycythemia vera, essential thrombocytopenia and myelofibrosis. Related compounds include:



Compound	R1	R2	R3	A	Formula
702749	OMe	H	4-[MeO(CH2)3]-1-Piz	CH	$C_{29}H_{32}N_4O_4$
702750	F	OMe	3(S)-[N(Me)2]-1-pyrrolidinyl	N	$C_{26}H_{26}FN_5O_3$

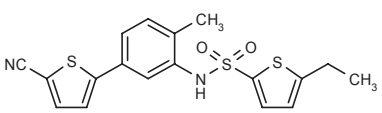
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Purandare, A.V. et al. (Bristol-Myers Squibb Co.) *Carbazole and carboline kinase inhibitors*. WO 2010080474.

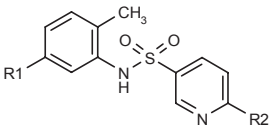
702920

N-[5-(5-Cyanothien-2-yl)-2-methylphenyl]-5-ethylthiophene-2-sulfonamide

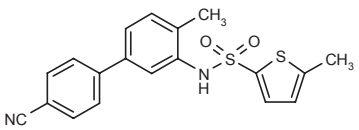


C18H16N2O2S3; Mol wt: 388.5270

ACTION – Hypoxia-inducible factor HIF-1α inhibitor that suppressed HIF-mediated transcription activation under hypoxic conditions (EC_{50} < 500 nM). It inhibited in vitro tubulin polymerization by 20-50% at 10 μM, and displayed antiproliferative activity against human breast adenocarcinoma MCF7 cells (EC_{50} < 500 nM). Reported to be useful for the treatment of cancer and other hyperproliferative disorders, as well as inflammation. Related compounds include:



Compound	R1	R2	Formula
702922	5-CN-2-thienyl	OMe	$C_{18}H_{15}N_3O_3S_2$
702932	5-CN-3-thienyl	OMe	$C_{18}H_{15}N_3O_3S_2$
702939	4-CN-3-MeO-Ph	OMe	$C_{21}H_{19}N_3O_4S$
702942	4-CN-Ph	Me	$C_{20}H_{17}N_3O_2S$
702946	5-CN-2-thienyl	Me	$C_{18}H_{15}N_3O_2S_2$



702937: C19H16N2O2S2

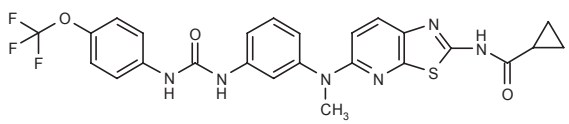
SOURCES – Elara Pharmaceuticals; European Molecular Biology Laboratory.

REFERENCES

1. Alonso, J. et al. (European Molecular Biology Laboratory;Elara Pharmaceuticals GmbH) *Toluidine sulfonamides and their use as inhibitors*. WO 2010076034, WO 2010085968.

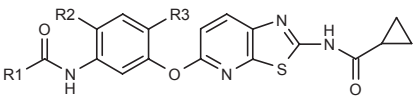
704133

N-[5-[*N*-Methyl-*N*-[3-[3-[4-(trifluoromethoxy)phenyl]ureido]-phenyl]amino]thiazolo[5,4-*b*]pyridin-2-yl]cyclopropanecarboxamide



C25H21F3N6O3S; Mol wt: 542.5330

ACTION – Serine/threonine-protein kinase B-raf inhibitor that showed antiproliferative activity against human colon adenocarcinoma HT-29 cancer cell (100% inhibition of cell growth at 5 μM; IC_{50} < 500 nM). Related compounds include:



Compound	R1	R2	R3	Formula
704134	6-CF3-3-Pyr-NH	F	H	$C_{23}H_{16}F_4N_6O_3S$
704135	3-thienyl-CH2	H	Me	$C_{23}H_{20}N_4O_3S_2$

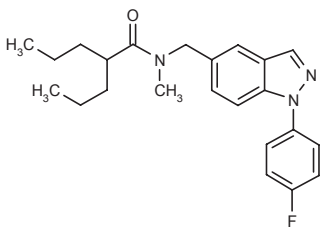
SOURCE – Takeda.

REFERENCES

1. Okaniwa, M. (Takeda Pharmaceutical Co., Ltd.) *Heterocyclic compound and use thereof*. WO 2010064611.

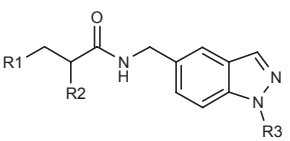
704243

N-[1-(4-Fluorophenyl)-1*H*-indazol-5-ylmethyl]-*N*-methyl-2-propyl-pentanamide



C23H28FN3O; Mol wt: 381.4863

ACTION – Smoothened homolog inhibitor potentially useful for the treatment of cancer, including basal cell carcinoma, medulloblastoma, and prostate, pancreas, breast, colon, bone, small cell lung and gastrointestinal cancers, among others. Related compounds include:



Compound	R1	R2	R3	Formula
704246	H	t-Bu	4-F-Ph	$C_{21}H_{24}FN_3O$
704247	Et	Pr	3-Me-2-Pyr	$C_{22}H_{28}N_4O$
704249	Et	Pr	4,6-(Me)2-2-pyrimidinyl	$C_{22}H_{29}N_5O$
704250	Et	Pr	imidazo[1,2-a]pyridin-6-yl	$C_{23}H_{27}N_5O$
704252	Et	Pr	2-F-3-Pyr	$C_{21}H_{25}FN_4O$
704253	Et	Pr	3-F-Ph	$C_{22}H_{26}FN_3O$
704257	Et	Pr	4-(NH2SO2)-Ph	$C_{22}H_{28}N_4O_3S$

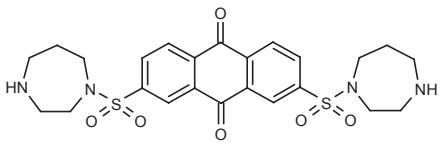
SOURCE – Istituto di Ricerche di Biologia Molecolare P. Angeletti, Pomezia (IT).

REFERENCES

1. Branca, D. et al. (Istituto di Ricerche di Biologia Molecolare P. Angeletti SpA) *Unsaturated bicyclic heterocyclic derivatives as Smo antagonists*. WO 2010082044.

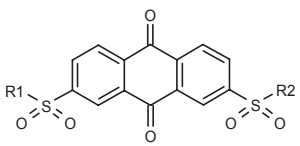
704275

2,7-Bis(perhydro-1,4-diazepin-1-ylsulfonyl)-9,10-anthraquinone

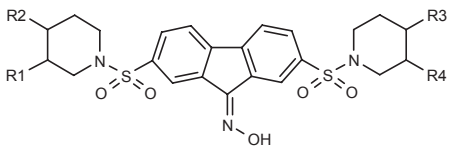


C24H28N4O6S2; Mol wt: 532.6320

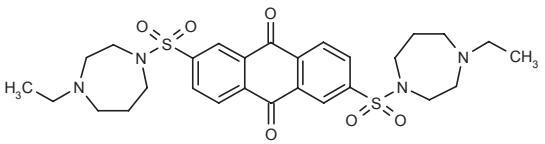
ACTION – Compound able to modulate gene expression in cancer cells that inhibited the growth of human colon adenocarcinoma HT-29 cells with an IC_{50} of < 1 μM. Other representative compounds are:



Compound	R1=R2	Formula
704279	4-Me-1-Piz	$C_{24}H_{28}N_4O_6S_2$
704288	NHCH2CH2N(Et)2	$C_{26}H_{36}N_4O_6S_2$
704290	perhydro-2-isoquinolyl	$C_{32}H_{38}N_2O_6S_2$
704291	1-adamantyl-NHCH2CH2NH	$C_{38}H_{48}N_4O_6S_2$



Compound	R1=R4	R2=R3	Formula
704295	H	Me	$C_{25}H_{31}N_3O_5S_2$
704297	CO2Et	H	$C_{29}H_{35}N_3O_9S_2$



704293: C28H36N4O6S2

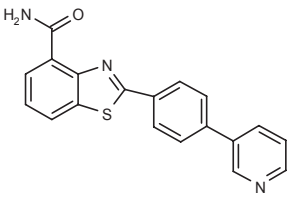
SOURCE – Avalon Pharmaceuticals.

REFERENCES

1. Cholody, W.M. et al. (Avalon Pharmaceuticals Inc.) *Derivatives of multi-ring aromatic compounds and uses as anti-tumor agents*. WO 2010082912.

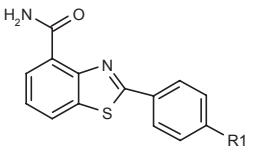
704304

2-[4-(3-Pyridyl)phenyl]benzothiazole-4-carboxamide



C19H13N3OS; Mol wt: 331.3910

ACTION – Poly(ADP-ribose)polymerase PARP-1 inhibitor (K_i = 9.5 nM), reported to be useful for the treatment of cancer. Related compounds include:



Compound	R1	Formula
704305	OSO2CF3	$C_{15}H_9F_3N_2O_4S_2$
704307	4-Pyr	$C_{19}H_{13}N_3OS$

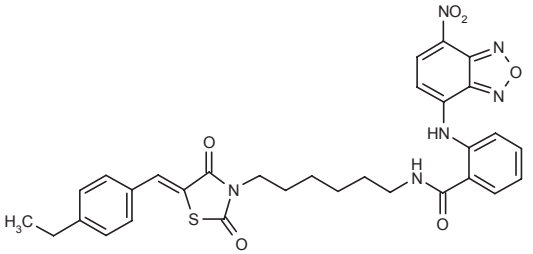
SOURCE – Abbott.

REFERENCES

1. Przytulinska, M.K. et al. (Abbott Laboratories Inc.) *Benzthiazole inhibitors of poly(ADP-ribose)polymerase*. US 2010183743, WO 2010083199.

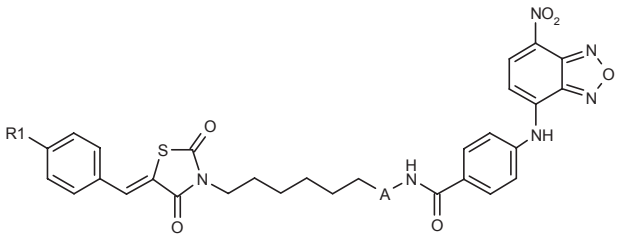
704373

N-[6-[5(*Z*)-(4-Ethylbenzylidene)-2,4-dioxothiazolidin-3-yl]hexyl]-2-(7-nitro-2,1,3-benzoxadiazol-4-ylamino)benzamide

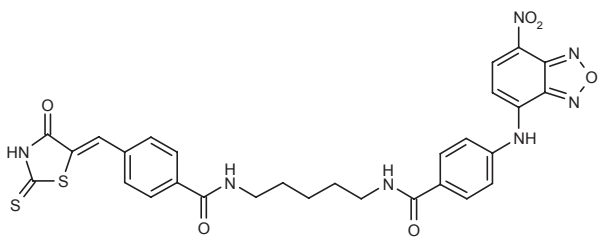


C31H30N6O6S; Mol wt: 614.6710

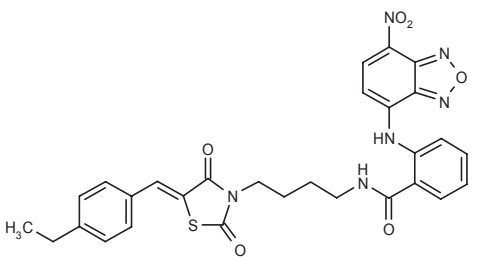
ACTION – Proto-oncogene c-Myc inhibitor (K_D = 2.2 nM) that disrupted the interaction between c-Myc and max and suppressed the growth of human leukemia HL-60 and Burkitt's lymphoma c-Myc-dependent cancer cell lines with IC_{50} values of 0.5-0.7 and 0.7-0.9 µM, respectively. Related compounds include:



Compound	R1	A	Formula
704376	Et	bond	$C_{31}H_{30}N_6O_6S$
704379	Et	-NHCOCH2-	$C_{33}H_{33}N_7O_7S$
704384	F	bond	$C_{29}H_{25}FN_6O_6S$



704374: C29H25N7O6S2



704381: C29H26N6O6S

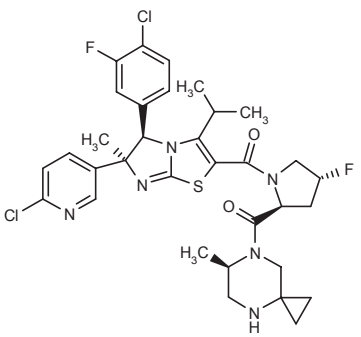
SOURCES – Georgetown University, Washington, DC (US); University of Pittsburgh, Pittsburgh, PA (US).

REFERENCES

1. Metallo, S. et al. (University of Pittsburgh;Georgetown University) *Linked Myc-Max small molecule inhibitors*. WO 2010083404.

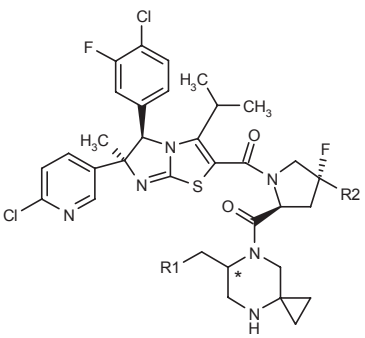
704507

1-[5(*R*)-(4-Chloro-3-fluorophenyl)-6(*S*)-(6-chloropyridin-3-yl)-3-isopropyl-6-methyl-5,6-dihydroimidazo[2,1-*b*]thiazol-2-yl]-1-[4(*R*)-fluoro-2(*S*)-[6(*R*)-methyl-4,7-diazaspiro[2.5]oct-7-ylcarbonyl]pyrrolidin-1-yl]methanone



C33H36Cl2F2N6O2S; Mol wt: 689.6460

ACTION – Compound that suppressed the interaction between oncoprotein Mdm2 and p53 (IC_{50} = 0.0039 µM) and inhibited the growth of p53-positive human lung cancer NCI-H460 cells (GI_{50} < 0.4 µM in an MTT assay). When administered to mice bearing bone sarcoma SJSA-1 or SJSA-1-RE at 50 mg/kg p.o. b.i.d. for 4 days it reduced tumor weight by 70-100%. Other representative compounds are:



Compound	R1	R2	*Isomer	Formula
704510	H	H	S	$C_{33}H_{36}Cl_2F_2N_6O_2S$
704511	Me	H	S	$C_{34}H_{38}Cl_2F_2N_6O_2S$
704513	Me	H	R	$C_{34}H_{38}Cl_2F_2N_6O_2S$
704514	H	F	S	$C_{33}H_{35}Cl_2F_3N_6O_2S$

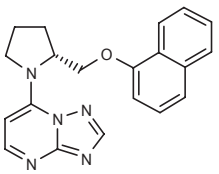
SOURCE – Daiichi Sankyo.

REFERENCES

1. Uoto, K. et al. (Daiichi Sankyo Co., Ltd.) *Imidazothiazole derivative having proline ring structure*. WO 2010082612.

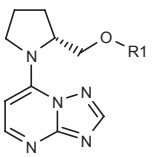
704661

7-[2(*R*)-(Naphthalen-1-yloxymethyl)pyrrolidin-1-yl][1,2,4]triazolo-[1,5-*a*]pyrimidine

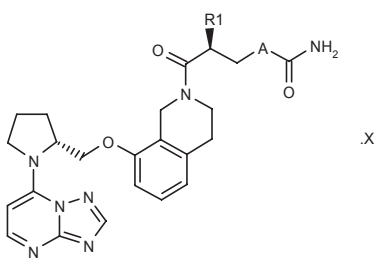


C20H19N5O; Mol wt: 345.3978

ACTION – Methionine aminopeptidase 2 inhibitor (IC_{50} = 10 nM-1 µM) claimed for use in the treatment of cancer, hemangioma, rheumatoid arthritis, atherosclerotic neovascularization, psoriasis, ocular neovascularization, osteoporosis, diabetes and obesity. Related compounds include:



Compound	R1	Formula
704662	6-CF3O-4-quinolyl	$C_{20}H_{17}F_3N_6O_2$
704663	1-isoquinolyl	$C_{19}H_{18}N_6O$
704664	1-(4-morpholinyl-CH2CH2NHCH2)-4-Naph	$C_{27}H_{33}N_7O_2$
704669	6-PhO-3-Pyr-CO	$C_{22}H_{20}N_6O_3$
704673	H	$C_{10}H_{13}N_5O$



Compound	R1	A	X	Formula
704665	AcNH	bond	formate	$C_{26}H_{32}N_8O_6$
704668	H	CH2		$C_{24}H_{29}N_7O_3$

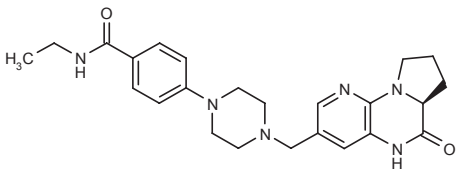
SOURCE – Merck KGaA.

REFERENCES

1. Heinrich, T. et al. (Merck Patent GmbH) *Novel heterocyclic compounds for use as MetAP-2 inhibitors*. DE 102009005193, WO 2010083870.

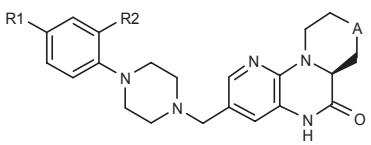
704760

N-Ethyl-4-[4-[(6a*S*)-6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-*e*]-pyrrolo[1,2-*a*]pyrazin-3-ylmethyl]piperazin-1-yl]benzamide

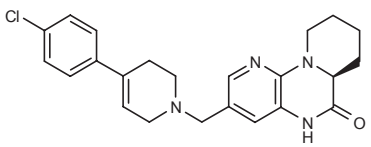


C24H30N6O2; Mol wt: 434.5340

ACTION – Poly(ADP-ribose)polymerase (PARP) inhibitor that gave a pK_d of > 7.5 in binding assays, inhibited PARP with a $pIC_{50} \geq 7.9$ and gave a potentiation factor (PF_{50}) > 5000 in a PARP chemopotentiation assay using Jurkat cells. Claimed for use in the treatment of cancer, cardiovascular disorders, metabolic diseases, inflammation, reperfusion injury, ischemic conditions and neurodegeneration. Other representative compounds are:



Compound	R1	R2	A	Formula
704765	CONHEt	F	S	$C_{24}H_{29}FN_6O_2S$
704766	cyclopropyl-NHCO	F	CH2	$C_{26}H_{31}FN_6O_2$
704768	CN	OMe	CH2	$C_{24}H_{28}N_6O_2$
704770	CONHMe	Cl	bond	$C_{23}H_{27}ClN_6O_2$
704772	CONHEt	Me	bond	$C_{25}H_{32}N_6O_2$



704763: C23H25ClN4O

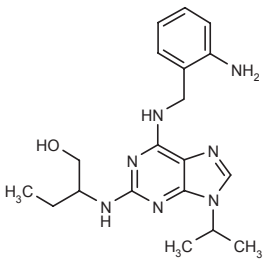
SOURCE – Takeda.

REFERENCES

1. Gangloff, A.R. et al. (Takeda Pharmaceutical Co., Ltd.) *Poly(ADP-ribose)polymerase (PARP) inhibitors*. US 2010190763, WO 2010085570.

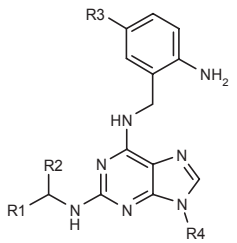
704977

2-[N^6-(2-Aminobenzyl)-9-isopropyladenin-2-ylamino]butan-1-ol



C19H27N7O; Mol wt: 369.4640

ACTION – Inhibitor of cyclin-dependent kinases, especially CDK1, CDK2 and CDK9 (IC_{50} = 0.09, 0.03 and 0.005 μM, respectively), that suppressed the replication of a panel of DNA and RNA viruses (IC_{50} = 2.4- > 20 μM). It prevented the proliferation of human breast carcinoma MCF7, erythroleukemia K-562, osteogenic sarcoma HOS, malignant melanoma G-361, T-lymphoblastoid leukemia CEM, promyelocytic leukemia HL-60 and cervical carcinoma HeLa cells (IC_{50} = 3.4, 12.8, 11, 8, 4.5, 6.7 and 2.5 μM, repectively), while showing much less activity against normal human fibroblasts (IC_{50} = 167 μM). In vivo compound prolonged survival and reduced body height in DBA-2 mice bearing leukemia P388D1 at 250 mg/kg p.o. and it reduced tumor volume in mice bearing human lung adenocarcinoma A549 xenografts at 150 mg/kg p.o. Expected to be useful for the treatment of cancer and viral infections. Further applications includes restenosis, psoriasis, rheumatoid arthritis and lupus, among others. Related compounds include:



Compound	R1	R2	R3	R4	Formula
704979	CH2OH	Et	H	Me	$C_{17}H_{23}N_7O$
704980	CH2OH	i-Pr	H	Me	$C_{18}H_{25}N_7O$
704989	C(Me)2OH	H	H	Me	$C_{17}H_{23}N_7O$
704991	CH2OH	Et	H	Et	$C_{18}H_{25}N_7O$
704992	CH2OH	i-Pr	H	Et	$C_{19}H_{27}N_7O$
704994	C(Me)2OH	H	H	i-Pr	$C_{19}H_{27}N_7O$
704995	CH2OH	Et	Cl	i-Pr	$C_{19}H_{26}ClN_7O$

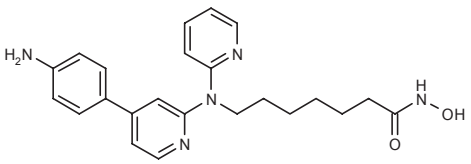
SOURCES – BioApex; Univerzita Palackého v Olomouci, Olomouc (CZ).

REFERENCES

1. Havlicek, L. et al. (Univerzita Palackého v Olomouci;BioApex, sro) *Substituted 6-(2-aminobenzylamino)purine derivatives, their use as medicaments and preparations containing these compounds*. WO 2010085924.

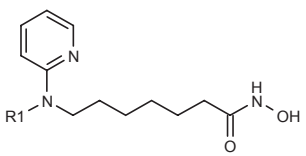
705180

7-[*N*-[4-(4-Aminophenyl)pyridin-2-yl]-*N*-(2-pyridyl)amino]heptanohydroxamic acid



C23H27N5O2; Mol wt: 405.4928

ACTION – Histone deacetylase inhibitor (IC_{50} = 0.298 μM in HeLa nuclear extracts) that displayed antiproliferative activity against human breast adenocarcinoma MCF7 cells (IC_{50} = 0.039 μM). Reported to be useful for the treatment of cancer, as well as cardiac hypertrophy, chronic heart failure and dermatological, gastrointestinal tract or musculoskeletal inflammatory disorders, and as an immunosuppressant. Further applications include the treatment of thalassemia, diabetes, osteoporosis, infections, fragile X syndrome, oral leukoplakia and CNS disorders. Other representative compounds are:



Compound	R1	Formula
705168	4-(3-MePh)-2-Pyr	$C_{24}H_{28}N_4O_2$
705170	4-(4-MePh)-2-Pyr	$C_{24}H_{28}N_4O_2$
705173	3-isoquinolyl	$C_{21}H_{24}N_4O_2$
705175	5-Ph-2-Pyr	$C_{23}H_{26}N_4O_2$
705178	2-quinolyl	$C_{21}H_{24}N_4O_2$

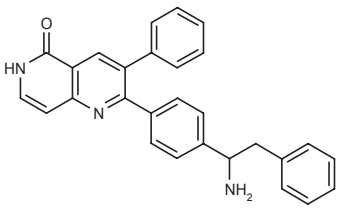
SOURCE – Karus Therapeutics.

REFERENCES

1. Shuttleworth, S.J. and Tomassi, C.D. (Karus Therapeutics Ltd.) *Scriptaid isosteres and their use in therapy*. WO 2010086646.

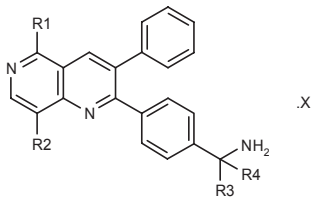
705556

2-[4-(1-Amino-2-phenylethyl)phenyl]-3-phenyl-1,6-naphthyridin-5(6*H*)-one

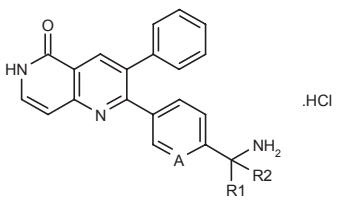


C28H23N3O; Mol wt: 417.5017

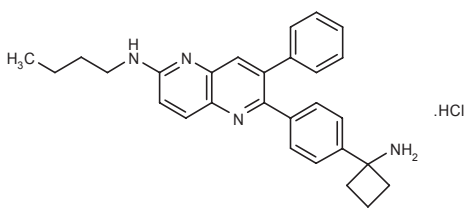
ACTION – Protein kinase B (PKB/Akt) inhibitor that suppressed c-Akt and/or Akt-2 and/or Akt-3 activity (IC_{50} < 50 μM). Reported to be useful for the treatment of cancer. Related compounds include:



Compound	R1	R2	R3	R4	X	Formula
705562	OH	2-F-Ph	H	H	TFA	$C_{29}H_{21}F_4N_3O_3$
705564	1,3,4-thiadiazol-2-yl-NH	H	-(CH2)3-			$C_{26}H_{22}N_6S$
705565	4-morpholinyl-CH2CH2O	H	H	H		$C_{27}H_{28}N_4O_2$
705566	3-(PhCH2O)-Ph	H	H	H		$C_{34}H_{27}N_3O$



Compound	R1	R2	A	Formula
705560	-(CH2)4-		CH	$C_{25}H_{24}ClN_3O$
705563	H	H	N	$C_{20}H_{17}ClN_4O$



705568: C28H31ClN4

SOURCES – Banyu; Merck & Co.

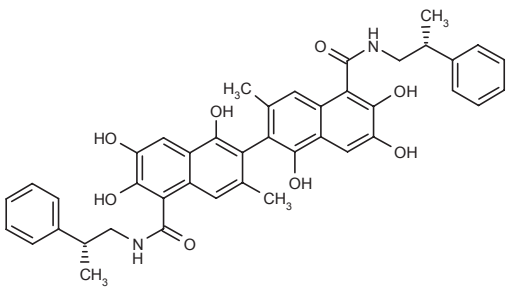
REFERENCES

1. Armstrong, D.J. et al. (Merck & Co., Inc.;Banyu Pharmaceutical Co., Ltd.) *Inhibitors of Akt activity*. WO 2010088177.

BI-97C1[2]

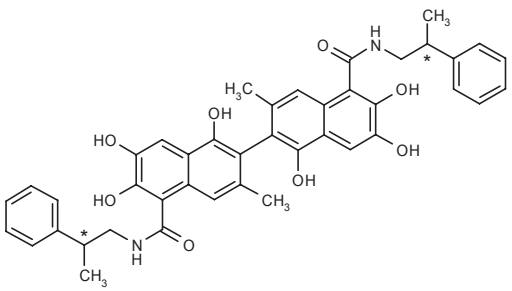
698375

(–)-1,1',6,6',7,7'-Hexahydroxy-3,3'-dimethyl-*N*,*N*'-bis[2(*R*)-phenylpropyl]-2,2'-binaphthalene-5,5'-dicarboxamide



C42H40N2O8; Mol wt: 700.7756

ACTION – Apogossypol derivative, an inhibitor of Bcl-XL (IC_{50} = 0.31 μM), Bcl-2 (IC_{50} = 0.32 μM), Mcl-1 (IC_{50} = 0.20 μM) and BFL-1 (IC_{50} = 0.62 μM) and the growth of human prostate PC-3, lung NCI-H460 and lymphoma BP-3 cancer cell lines (EC_{50} = 0.13, 0.42 and 0.049 μM, respectively). Compound produced almost complete inhibition of tumor growth in athymic nude mice bearing human prostate tumor M2182 xenografts at 5 mg/kg i.p. every 2 days. Other related compounds are:



Compound	*Isomer	Formula
668452[1,2]		$C_{42}H_{40}N_2O_8$
698372[2]	(+), S	$C_{42}H_{40}N_2O_8$

SOURCES – Coronado Biosciences; Sanford-Burnham Medical Research Institute, La Jolla, CA (US); Virginia Commonwealth University, Richmond, VA (US).

REFERENCES

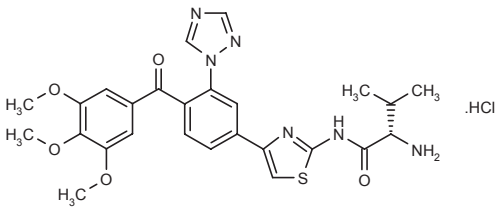
1. Wei, J. et al. *Apogossypol derivatives as pan-active inhibitors of antiapoptotic B-cell lymphoma/leukemia-2 (Bcl-2) family proteins*. J Med Chem 2009, 52(14): 4511.

2. Wei, J. et al. *BI-97C1, an optically pure apogossypol derivative as pan-active inhibitor of antiapoptotic B-cell lymphoma/leukemia-2 (Bcl-2) family proteins*. J Med Chem 2010, 53(10): 4166.

CKD-516[1,3-8]

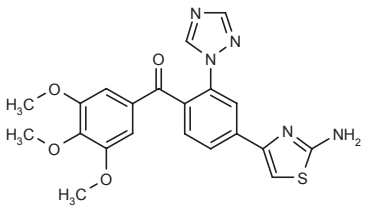
652479

N-[4-[3-(1*H*-1,2,4-Triazol-1-yl)-4-(3,4,5-trimethoxybenzoyl)phenyl]-thiazol-2-yl]-L-valinamide hydrochloride



C26H29ClN6O5S; Mol wt: 573.0640

ACTION – Prodrug of the tubulin polymerization inhibitor **S-516** (IC_{50} = 4.29 μM; cytotoxic IC_{50} = 4.8-24.9 nM against human leukemia HL-60, colon carcinoma HCT 116 and colon adenocarcinoma HCT-15 cells) that inhibited the growth of human HCT 116 and HCT-15 and murine colon tumor CT26 and Lewis lung carcinoma xenografts in mice by 65, 69, 55 and 68%, respectively, at 10 mg/kg i.p. Phase I clinical trials are ongoing in patients with advanced solid tumors.



S-516 [658266][1,2,4,6]: C21H19N5O4S

SOURCE – Chong Kun Dang Pharm (CKD Pharm).

REFERENCES

1. Choi, N.-S. et al. (Chong Kun Dang Pharmaceutical Corp.) *Benzophenone thiazole derivatives useful for inhibiting formation of microtubule and method for producing the same*. WO 2009119980.

2. Kim, Y.-H. et al. (Chong Kun Dang Pharmaceutical Corp.) *Benzophenone derivatives useful for inhibiting formation of microtubule*. EP 2066632, US 2009275575, WO 2008038955.

3. Kim, S.J. et al. *Oral efficacy and preclinical ADME evaluation of CKD-516, a novel tubulin polymerization inhibitor*. Proc Am Assoc Cancer Res (AACR) 2010, 51: Abst 4425.

4. Lee, J. et al. *Discovery of a potent tubulin polymerization inhibitor: Synthesis and evaluation of water-soluble prodrugs of benzophenone analog*. Bioorg Med Chem Lett 2010, 20(21): 6327.

5. Lee, J. et al. *Identification of CKD-516: A potent tubulin polymerization inhibitor with marked antitumor activity against murine and human solid tumors*. J Med Chem 2010, 53(17): 6337.

6. Lee, K.J. et al. *CKD-516, a novel tubulin-binding agent shows marked antitumor activity against murine and human solid tumors*. Proc Am Assoc Cancer Res (AACR) 2009, 50: Abst 5561.

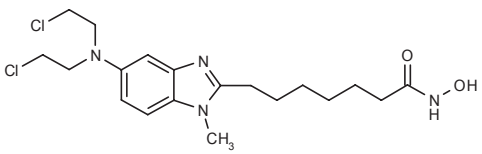
7. *Product in development*. Chong Kun Dang Pharmaceutical Corp. Web Site 2009, Feb 17.

8. *Safety study of increasing doses of CKD-516 in patients with advanced solid cancers (NCT01028859)*. ClinicalTrials.gov Web Site 2009, Dec 16.

CY-190602

704660

7-[5-[*N*,*N*-Bis(2-chloroethyl)amino]-1-methyl-1*H*-benzimidazol-2-yl]heptanohydroxamic acid



C19H28Cl2N4O2; Mol wt: 415.3570

ACTION – Histone deacetylase inhibitor that suppressed HD1, 2, 3, 6, 8 and 10 with respective IC_{50} values of 17, 9, 25, 6, 107 and 72 nM. Compound showed antiproliferative activity against human myeloma RPMI 8226, MM1.R and MM1.S cells (IC_{50} = 4.16, 2.66 and 1.6 μM, respectively). Claimed for use in the treatment of neoplastic diseases such as cancer and immunological disorders.

SOURCE – Crystal Biopharmaceutical.

REFERENCES

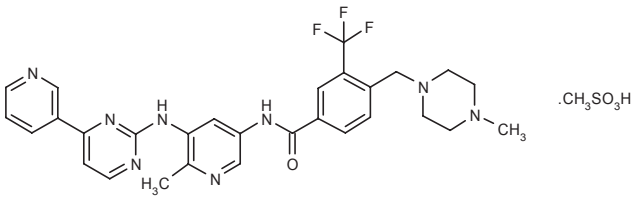
1. Chen, Y. and Chen, Y. (Crystal Biopharmaceutical LLC) *Hydroxamic acid derivatives*. WO 2010085377.

FLUMATINIB MESYLATE

702641

4-(4-Methylpiperazin-1-ylmethyl)-*N*-[6-methyl-5-[4-(3-pyridyl)-pyrimidin-2-ylamino]pyridin-3-yl]-3-(trifluoromethyl)benzamide methanesulfonate

HH-GV-678
HHGV-678



C30H33F3N8O4S; Mol wt: 658.6940

ACTION – A structural of the BCR/ABL kinase inhibitor imatinib mesilate[+] that inhibited the proliferation of human leukemia K-562 cells (IC_{50} = 0.008 μM) more potently than imatinib (IC_{50} = 0.33 μM); compound completely eliminated K-562 tumors in 4 of 6 and 7 of 8 mice at 75 mg/kg p.o. for 21 days and in all 8 animals at 150 mg/kg p.o. for 21 days. Currently in phase I trials for chronic myelogenous leukemia.

SOURCES – Shanghai Hengrui; Shanghai Institute of Materia Medica, Shanghai, (CN).

REFERENCES

1. Yang, B. et al. *Aminopyrimidine compounds and their salts, process for preparation and pharmaceutical use thereof*. CA 2602738, CN 1939910, CN 1972917, EP 1840122, JP 2008526692, US 2008312251, WO 2006069525.

2. Gong, A. et al. *Metabolism of flumatinib, a novel antineoplastic tyrosine kinase inhibitor, in chronic myelogenous leukemia patients*. Drug Metab Dispos 2010, 38(8): 1328.

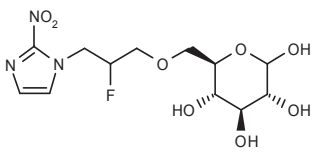
3. Qiu, L et al. *Effect of a novel tyrosine kinase inhibitor HHGV678 on growth inhibition of Bcr-Abl wild type and IM-resistant cell lines in vitro*. J Exp Hematol 2008, 16(5): 1039.

[+]Drug Data Rep 1997, 019(08): 0747; Drug Data Rep 2001, 023(07): 0711.

GAZ-F

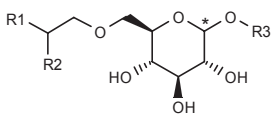
701267

6-*O*-[2-Fluoro-3-(2-nitro-1*H*-imidazol-1-yl)propyl]-D-glucopyranose

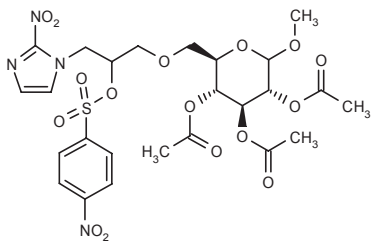


C12H18FN3O8; Mol wt: 351.2850

ACTION – Compound that actively permeates cell membranes via specific hypoxia-upregulated transporters, shown to radiosensitize human cervical carcinoma HeLa, mouse mammary tumor EMT6 and human glicoblastoma multiforme M006X cells at 0.5 mM. It also showed cytotoxic activity against EMT6, HeLa, M006X, mouse embryo K-BALB and K-BALB-STK cancer cells in MTT assays. Compound inhibited GLUT-1 and GLUT-2 transporters in *Xenopus laevis* oocytes and it showed a maximum tolerated dose > 900 mg/kg i.p. in BALB/c mice. Potentially useful for the treatment of tumors and for imaging hypoxic tissue. Other representative compounds are:



Compound	R1	R2	R3	*Isomer	Formula
GAZ-OH [701271]	2-NO2-1-imidazolyl-CH2	OH	H		$C_{12}H_{19}N_3O_9$
GAZ-V [701273]	(E)-2-NO2-1-imidazolyl-CH=	H	H		$C_{12}H_{17}N_3O_8$
701276	1,4-dioxido-1,2,4-benzotriazin-3-yl-NHCH2	OH	Me	S	$C_{17}H_{24}N_4O_9$
701277	1,4-dioxido-1,2,4-benzotriazin-3-yl-NHCH2	OH	H		$C_{16}H_{22}N_4O_9$



701269: C25H30N4O16S

SOURCE – University of Alberta, Edmonton, AB (CA).

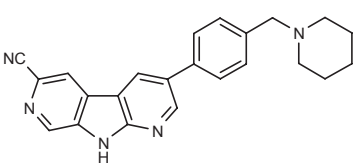
REFERENCES

1. Weibe, L.I. et al. (University of Alberta) *Compounds useful in delivering anti-neoplastic therapy and diagnostic imaging to hypoxic cells and methods of use thereof*. WO 2010073126.

GNE-900[1-3]

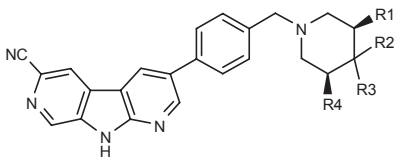
706154

3-[4-(Piperidin-1-ylmethyl)phenyl]-9*H*-pyrrolo[2,3-*b*:5,4-*c*']dipyridine-6-carbonitrile

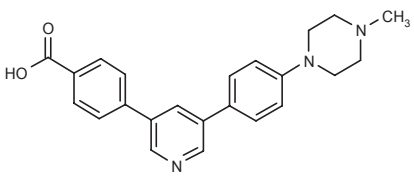


C23H21N5; Mol wt: 367.4463

ACTION – Serine/threonine-protein kinase Chk1 Inhibitor (IC_{50} = 1 nM) with reduced activity against acetylcholinesterase, CDK1/cyclin B, CDK2/cyclin A, KDR, GSK-3β and the hERG channel (IC_{50} = 333, 706, 366, 59.5, 44.3 and 12,600 nM, respectively). Compound inhibited tumor growth in mice bearing human colon cancer HT-29 xenografts after administration of gemcitabine. Oral bioavailability was 87, 67 and 44%, respectively in mice, rats and monkeys. Other related compounds are:



Compound	R1=R4	R2	R3	Formula
706165[2]	Me	H	H	$C_{25}H_{25}N_5$
706166[1-3]	H	-CH2OCH2-		$C_{25}H_{23}N_5O$



706164[1,2]**:** C23H23N3O2

SOURCE – Genentech.

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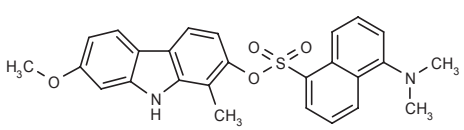
KED-4-69

674467

5-(Dimethylamino)naphthalene-1-sulfonic acid 7-methoxy-1-methyl-9*H*-carbazol-2-yl ester



C26H24N2O4S; Mol wt: 460.5450

ACTION – DNA methyltransferase inhibitor that increased RASSF1 expression and reduced cyclin D1 expression in human prostate cancer cells; it inhibited prostate cancer PC-3 cell growth (GI_{50} = 1.5 µM). In mice bearing PC-3 tumor xenografts it reduced tumor volume 40% at 10 mg/kg/day i.p. over 28 days, with no toxicity at up to 550 mg/kg. p.o.

SOURCE – Georgetown University, Washington, DC (US).

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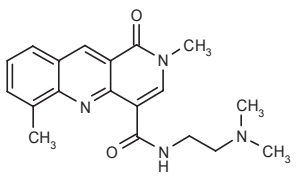
SN-28049*[1-6]

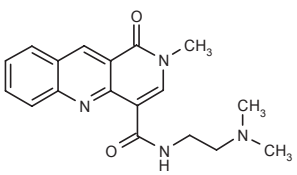
333042

N-[2-(Dimethylamino)ethyl]-2,6-dimethyl-1-oxo-1,2-dihydrobenzo-[*b*]-1,6-naphthyridine-4-carboxamide



C19H22N4O2; Mol wt: 338.4036

ACTION – DNA-binding agent that inhibited the growth of human lung carcinoma NCI-H460, murine leukemia P388, Lewis lung carcinoma and human leukemia Jurkat cells (IC_{50} = 8.8 2.1, 1.7 and 6.7 nM, respectively) and human fibrosarcoma cells (IC_{50} = 13 and 6.7 nM, respectively in the presence and absence of tetracycline). Compound produced 100% cure in mice bearing s.c. colon 38 tumors at doses of 3.9-8.9 mg/kg i.p., with tumor growth delay of > 20 days. Oral bioavailability was 54% in mice. Another related compound is:



SN-28507 [698008][1,3,6]**:** C18H20N4O2

SOURCES – University of Auckland, Auckland (NZ); La Trobe University, Melbourne (AU).

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*Identified compound **333042** Drug Data Rep 2003, 025(04): 0378.

BIOLOGICS FOR CANCER THERAPY

SIPULEUCEL-T

USAN

259673

Specific active immunotherapeutic composed of antigen-loaded autologous antigen-presenting cells designed to stimulate a T-cell immune response specific for the tumor-associated antigen prostatic acid phosphatase

Autologous dendritic cell product composed of antigen-presenting cells loaded ex vivo with the recombinant fusion protein PA2024, consisting of prostatic acid phosphatase linked to human granulocyte–macrophage colony-stimulating factor (GM-CSF)

APC-8015
APC-8015F

ACTION – Specific active immunotherapeutic composed of antigen-loaded autologous antigen-presenting cells designed to stimulate a T-cell immune response specific for the tumor-associated antigen prostatic acid phosphatase.

INDICATION – Treatment of asymptomatic or minimally symptomatic, metastatic, castrate-resistant (hormone-refractory) prostate cancer.

PRESENTATION – 250-mL suspension containing a minimum of 50 million autologous $CD54^+$ cells activated with PAP-GM-CSF in Lactated Ringer's Injection, USP, and supplied in an infusion bag labeled for the specific recipient.

PROPRIETARY NAME – *Provenge* (US).

SOURCE – Dendreon.

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121. *Vaccine therapy in treating patients with metastatic prostate cancer that has not responded to hormone therapy (NCT00005947)*. ClinicalTrials.gov Web Site 2005, Oct 7.

MONOGRAPH – McIntyre, J.A. and Fernández, D. *Provenge*. Drugs Fut 2005, 30(9): 0892.

OCULAR MEDICATIONS

MISCELLANEOUS OCULAR MEDICATIONS

PARSTATIN

264856

Methionyl-glycyl-prolyl-arginyl-arginyl-leucyl-leucyl-leucyl-valyl-alanyl-alanyl-cysteinyl-phenylalanyl-seryl-leucyl-cysteinyl-glycyl-prolyl-leucyl-leucyl-seryl-alanyl-arginyl-threonyl-arginyl-alanyl-arginyl-arginyl-prolyl-glutamyl-seryl-lysyl-alanyl-threonyl-asparaginyl-alanyl-threonyl-leucyl-aspartyl-prolyl-arginine

Human peptide of 41 amino acids naturally generated by cleavage of the N-terminal domain of the protease-activated receptor PAR1

Parstatin peptide
TR(1-41)[+]

C191H330N64O53S3; Mol wt: 4467.2560

ACTION – Thrombin receptor agonist peptide that inhibited VEGF- and bFGF-induced angiogenesis, and suppressed retinal neovascularization (60% at 3 µg intravitreally), choroidal neovascularization (IC_{50} = 3 µg intravitreally) and corneal neovascularization (59% at 200 µg subconjunctivally), respectively, in an oxygen-induced ischemic retinopathy mouse model, a laser-induced Bruch's membrane rupture mouse model and a chemical burn rat model. It also conferred cardioprotection in a rat model of ischemia-reperfusion injury.

SOURCES – Johns Hopkins University School of Medicine, Baltimore, MD (US); University of Massachusetts, Boston, MA (US); Medical College of Wisconsin, Milwaukee, WI (US); University of Patras, Patras (GR).

REFERENCES

1. Furman, M.I. et al. (University of Massachusetts) *Thrombin receptor peptides and uses thereof*. WO 1998016548.

2. Tsopanoglou, N.E. and Maragoudakis, M.E. *Bioactive parstatin peptides and methods of use*. US 2008242613.

3. Claytor, R.B. et al. *The cleaved peptide of PAR1 is a more potent stimulant of platelet-endothelial cell adhesion than is thrombin*. J Vasc Surg 2003, 37(2): 440.

4. Duncan, M.B. and Kalluri, R. *Parstatin, a novel protease-activated receptor 1-derived inhibitor of angiogenesis*. Mol Interv 2009, 9(4): 168.

5. Furman, M.I. et al. *The cleaved peptide of PAR1 results in a redistribution of the platelet surface GPIb-IX-V complex to the surface-connected canalicular system*. Thromb Haemost 2000, 84(5): 897.

6. Furman, M.I. et al. *The cleaved peptide of the thrombin receptor is a strong platelet agonist*. Proc Natl Acad Sci USA 1998, 95(6): 3082.

7. Huang, H. et al. *Parstatin suppresses ocular neovascularization and inflammation*. Invest Ophthalmol Vis Sci 2010, Adv. Publication.

8. Liu, L. et al. *Binding of thrombin to the G-protein-linked receptor, and not to glycoprotein Ib, precedes thrombin-mediated platelet activation*. J Biol Chem 1997, 272(3): 1997.

9. Ofosu, F.A. et al. *A trypsin-like platelet protease propagates protease-activated receptor-1 cleavage and platelet activation*. Biochem J 1998, 336(Part 2): 283.

10. Strande, J.L. et al. *Parstatin: A cryptic peptide involved in cardioprotection after ischaemia and reperfusion injury*. Cardiovasc Res 2009, 83(2): 325.

11. Vasilakis, P. et al. *The role of parstatin in ocular angiogenesis*. 8th Int Symp Ocular Pharmacol Ther (ISOPT) (Dec 3-6, Rome) 2009, Abst.

12. Zania, P. et al. *Parstatin, the cleaved peptide on proteinase-activated receptor 1 activation, is a potent inhibitor of angiogenesis*. J Pharmacol Exp Ther 2009, 328(2): 378.

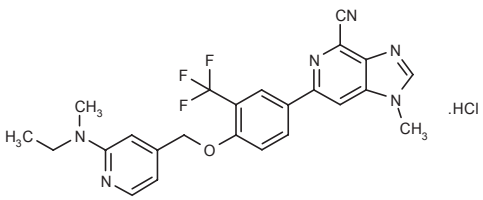
[+]Drug Data Rep 1998, 020(09): 0776.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

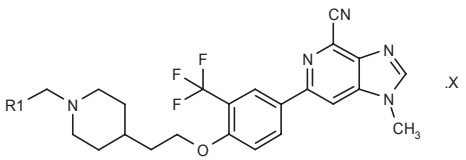
704259[1,2]

6-[4-[2-(*N*-Ethyl-*N*-methylamino)pyridin-4-ylmethoxy]-3-(trifluoromethyl)phenyl]-1-methyl-1*H*-imidazo[4,5-*c*]pyridine-4-carbonitrile hydrochloride



C24H22ClF3N6O; Mol wt: 502.9190

ACTION – Cathepsin S and/or cathepsin K inhibitor (pIC_{50} > 7 and < 7, respectively) that blocked cathepsin S and antigen presentation in human B lymphoblastoma cells (pEC_{50} > 7). Potentially useful for the treatment of osteoporosis, atherosclerosis, inflammation and immune disorders such as rheumatoid arthritis, psoriasis and neuropathic pain. Related compounds include:



Compound	R1	X	Formula
704251[1]	CON(Me)2	TFA	$C_{28}H_{30}F_6N_6O_4$
704254[1]	3,5-(Me)2-4-isoxazolyl		$C_{28}H_{29}F_3N_6O_2$
704255[1]	5-Me-3-isoxazolyl		$C_{27}H_{27}F_3N_6O_2$
704256[1]	2-oxazolyl	HCl	$C_{26}H_{26}ClF_3N_6O_2$

OCULAR MEDICATIONS

MISCELLANEOUS OCULAR MEDICATIONS

PARSTATIN

264856

Methionyl-glycyl-prolyl-arginyl-arginyl-leucyl-leucyl-leucyl-valyl-alanyl-alanyl-cysteinyl-phenylalanyl-seryl-leucyl-cysteinyl-glycyl-prolyl-leucyl-leucyl-seryl-alanyl-arginyl-threonyl-arginyl-alanyl-arginyl-arginyl-prolyl-glutamyl-seryl-lysyl-alanyl-threonyl-asparaginyl-alanyl-threonyl-leucyl-aspartyl-prolyl-arginine

Human peptide of 41 amino acids naturally generated by cleavage of the N-terminal domain of the protease-activated receptor PAR1

Parstatin peptide
TR(1-41)[+]

C191H330N64O53S3; Mol wt: 4467.2560

ACTION – Thrombin receptor agonist peptide that inhibited VEGF- and bFGF-induced angiogenesis, and suppressed retinal neovascularization (60% at 3 µg intravitreally), choroidal neovascularization (IC_{50} = 3 µg intravitreally) and corneal neovascularization (59% at 200 µg subconjunctivally), respectively, in an oxygen-induced ischemic retinopathy mouse model, a laser-induced Bruch's membrane rupture mouse model and a chemical burn rat model. It also conferred cardioprotection in a rat model of ischemia-reperfusion injury.

SOURCES – Johns Hopkins University School of Medicine, Baltimore, MD (US); University of Massachusetts, Boston, MA (US); Medical College of Wisconsin, Milwaukee, WI (US); University of Patras, Patras (GR).

REFERENCES

1. Furman, M.I. et al. (University of Massachusetts) *Thrombin receptor peptides and uses thereof*. WO 1998016548.

2. Tsopanoglou, N.E. and Maragoudakis, M.E. *Bioactive parstatin peptides and methods of use*. US 2008242613.

3. Claytor, R.B. et al. *The cleaved peptide of PAR1 is a more potent stimulant of platelet-endothelial cell adhesion than is thrombin*. J Vasc Surg 2003, 37(2): 440.

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10. Strande, J.L. et al. *Parstatin: A cryptic peptide involved in cardioprotection after ischaemia and reperfusion injury*. Cardiovasc Res 2009, 83(2): 325.

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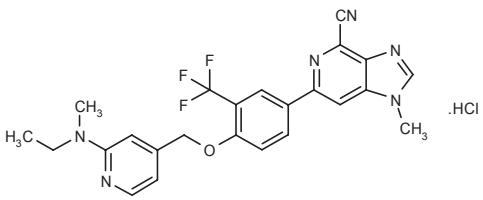
[+]Drug Data Rep 1998, 020(09): 0776.

METABOLIC DRUGS

TREATMENT OF BONE DISEASES

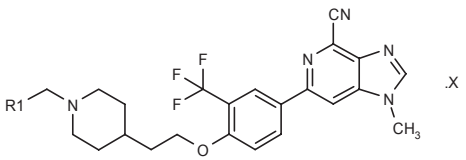
704259[1,2]

6-[4-[2-(*N*-Ethyl-*N*-methylamino)pyridin-4-ylmethoxy]-3-(trifluoromethyl)phenyl]-1-methyl-1*H*-imidazo[4,5-*c*]pyridine-4-carbonitrile hydrochloride



C24H22ClF3N6O; Mol wt: 502.9190

ACTION – Cathepsin S and/or cathepsin K inhibitor (pIC_{50} > 7 and < 7, respectively) that blocked cathepsin S and antigen presentation in human B lymphoblastoma cells (pEC_{50} > 7). Potentially useful for the treatment of osteoporosis, atherosclerosis, inflammation and immune disorders such as rheumatoid arthritis, psoriasis and neuropathic pain. Related compounds include:



Compound	R1	X	Formula
704251[1]	CON(Me)2	TFA	$C_{28}H_{30}F_6N_6O_4$
704254[1]	3,5-(Me)2-4-isoxazolyl		$C_{28}H_{29}F_3N_6O_2$
704255[1]	5-Me-3-isoxazolyl		$C_{27}H_{27}F_3N_6O_2$
704256[1]	2-oxazolyl	HCl	$C_{26}H_{26}ClF_3N_6O_2$

SOURCE – Merck & Co.

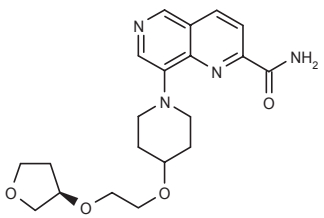
REFERENCES

1. Cai, J. et al. (NV Organon) *6-Phenyl-1H-imidazo[4,5-c]pyridine-4-carbonitrile derivatives as cathepsin S and/or cathepsin K inhibitors*. WO 2010081859.

2. Robinson, J.S. et al. (NV Organon) *6-Phenyl-1H-imidazo[4,5-c]pyridine-4-carbonitrile derivatives*. US 2010184761.

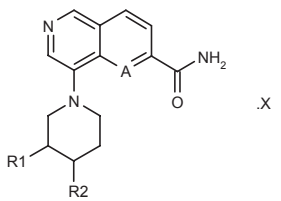
704495

8-[4-[2-[Tetrahydrofuran-3(*R*)-yloxy]ethoxy]piperidin-1-yl]-1,6-naphthyridine-2-carboxamide

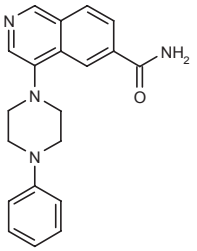


C20H26N4O4; Mol wt: 386.4448

ACTION – Compound that increased alkaline phosphatase activity by at least 200% at 0.03 µg/mL in an osteoblast differentiation test using bone marrow-derived stromal ST2 cells. When administered to ovariectomized F344 rats at 3 mg/kg p.o. it significantly increased bone density in femora. Reported to be useful for the treatment of bone diseases, particularly osteoporosis. Related compounds include:



Compound	R1	R2	A	X	Formula
704496	H	3(S)-THF-OCH2CH2O	N		$C_{20}H_{26}N_4O_4$
704497	H	4-THP-OCH2CH2O	N	HCl	$C_{21}H_{29}ClN_4O_4$
704498	H	H	N		$C_{14}H_{16}N_4O$
704500	CH2OMe	H	CH		$C_{17}H_{21}N_3O_2$



704499: C20H20N4O

SOURCE – Daiichi Sankyo.

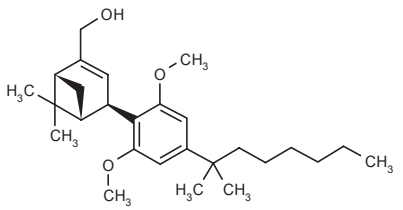
REFERENCES

1. Kanno, O. et al. (Daiichi Sankyo Co., Ltd.) *Cyclic compound having hetero atom*. WO 2010082563.

HU-433

692745

1-[(1*R*,4*R*,5*R*)-4-[2,6-Dimethoxy-4-(2-methyloctan-2-yl)phenyl]-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl]methanol



C27H42O3; Mol wt: 414.6206

ACTION – Selective cannabinoid CB2 receptor agonist (K_i = 7.9 nM and > 5 µM, respectively, for CB2 and CB1 receptors) that stimulated mouse osteoblast number at 0.01 nM and rescued ovariectomy-induced bone loss in mice at 0.2 mg/kg/day i.p. Potentially useful for the treatment of osteoporosis.

SOURCE – Hebrew University, Jerusalem (IL).

REFERENCES

1. Bab, I. et al. (Yissum Research Development Co.) *Compositions comprising CB receptor agonists, uses thereof and methods for their preparation*. WO 2010041253.

2. Bab, I. *CB2 regulation of bone metabolism in health and disease*. 20th Symp Int Cannabinoid Res Soc (July 23-27, Lund) 2010, Abst.

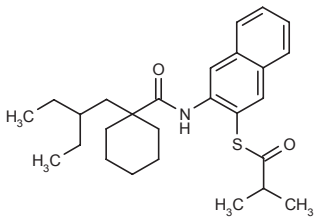
3. Bab, I. and Mechoulam, R. *Non-Psychotropic cannabinoid treatment for osteoporosis*. 8th ILSI-Biomed Annu Conf (June 15-17, Tel-Aviv) 2009, Abst.

4. Smoum, R. et al. *HU-433, enantiomer of the CB2 agonist HU-308, is a highly potent regulator of bone mass*. 20th Symp Int Cannabinoid Res Soc (July 23-27, Lund) 2010, Abst P2-25.

TREATMENT OF LIPOPROTEIN DISORDERS

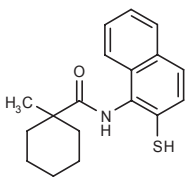
700247

2-Methylpropanethioic acid *S*-[3-[1-(2-ethylbutyl)cyclohexylcarboxamido]naphthalen-2-yl] ester



C27H37NO2S; Mol wt: 439.6530

ACTION – Cholesteryl ester transfer protein inhibitor reported to be useful for the treatment of dyslipidemia. Further applications include atherosclerosis, peripheral vascular disease, hyper-α-lipoproteinemia, hyper-β-lipoproteinemia, angina, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, diabetes, obesity and endotoxemia, among others. Another exemplified compound is:



700248: C18H21NOS

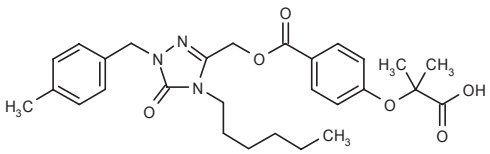
SOURCE – Roche.

REFERENCES

1. Hoffmann, T. et al. (F. Hoffmann-La Roche AG) *Cyclohexanecarboxamide derivatives useful as inhibitors of cholesteryl ester transfer protein*. US 2010160441, WO 2010069859.

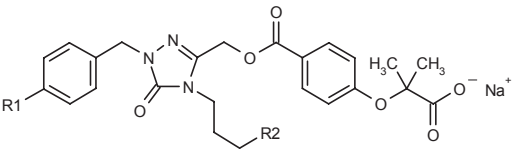
700627

2-[4-[4-Hexyl-1-(4-methylbenzyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-ylmethoxycarbonyl]phenoxy]-2-methylpropionic acid

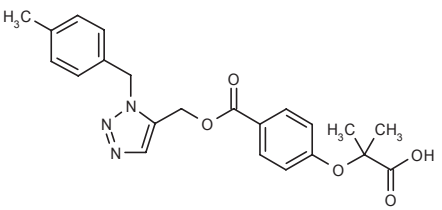


C28H35N3O6; Mol wt: 509.5940

ACTION – Peroxisome proliferator-activated receptor PPARα agonist that activated human Gal-4PPARα (EC_{50} = 1-50 nM) selectively over human Gal-4PPARγ, β and δ (EC_{50} > 1 μM). Reported to be useful for the treatment of dyslipidemia, particularly hypercholesterolemia, primary hypercholesterolemia or mixed dyslipidemia, hypertriglyceridemia, hyperlipidemia type IV or V, as well as atherosclerosis. Related compounds include:



Compound	R1	R2	Formula
700614	t-Bu	H	$C_{28}H_{34}N_3NaO_6$
700622	Me	C5H11	$C_{30}H_{38}N_3NaO_6$



700618: C22H23N3O5

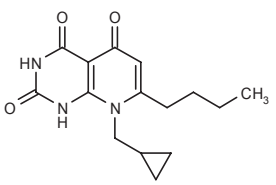
SOURCE – ARYx Therapeutics.

REFERENCES

1. Luehr, G.W. et al. (ARYx Therapeutics, Inc.) *Agonists of peroxisome proliferator activated receptor-alpha*. US 2010184815, WO 2010071813.

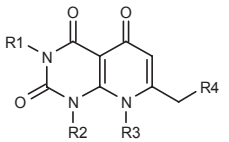
701314

7-Butyl-8-(cyclopropylmethyl)pyrido[2,3-*d*]pyrimidine-2,4,5(1*H*,3*H*,8*H*)-trione



C15H19N3O3; Mol wt: 289.3297

ACTION – Nicotinic acid receptor agonist expected to be useful for the treatment of dyslipidemia, type 2 diabetes and obesity. Further applications include cardiovascular, neurological and hematological disorders, cancer, inflammation, respiratory diseases, gastroenterological diseases and nonalcoholic fatty liver disease. Related compounds include:



Compound	R1=R2	R3	R4	Formula
701315	H	CH2CH2OMe	Pr	$C_{14}H_{19}N_3O_4$
701316	H	allyl	cyclopropyl-CH2CH2	$C_{16}H_{19}N_3O_3$
701317	allyl	CH2F	Pr	$C_{18}H_{22}FN_3O_3$
701318	allyl	CHF2	cyclopropyl-CH2CH2	$C_{20}H_{23}F_2N_3O_3$
701320	H	CH2CH2F	Pr	$C_{13}H_{16}FN_3O_3$
701323	H	allyl	Pr	$C_{14}H_{17}N_3O_3$
701327	H	Bu	1-Naph	$C_{22}H_{21}N_3O_3$

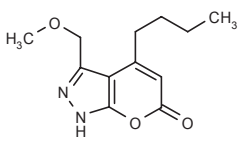
SOURCE – Merck & Co.

REFERENCES

1. Xiao, D. et al. (Schering Corp.) *Pyridopyrimidine derivatives and methods of use thereof*. WO 2010075068.

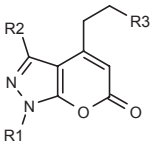
701348

4-Butyl-3-(methoxymethyl)pyrano[2,3-*c*]pyrazol-6(1*H*)-one

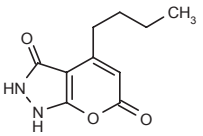


C12H16N2O3; Mol wt: 236.2670

ACTION – Nicotinic acid receptor agonist reported to be useful for the treatment of dyslipidemia, type 2 diabetes and obesity. Further applications include cardiovascular, neurological and hematological disorders, cancer, inflammation, respiratory diseases, gastroenterological diseases and nonalcoholic fatty liver disease. Related compounds include:



Compound	R1	R2	R3	Formula
701373	H	Me	H	$C_9H_{10}N_2O_2$
701377	Ph	CO2Et	H	$C_{17}H_{16}N_2O_4$
701379	H	CF3	Et	$C_{11}H_{11}F_3N_2O_2$
701380	H	CF3	allyl	$C_{12}H_{11}F_3N_2O_2$
701382	H	CF3	cyclopropyl-CH2	$C_{13}H_{13}F_3N_2O_2$
701394	H	CHF2	Et	$C_{11}H_{12}F_2N_2O_2$



701389: C10H12N2O3

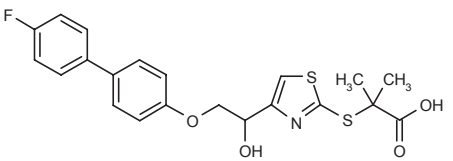
SOURCE – Merck & Co.

REFERENCES

1. Xiao, D. et al. (Schering Corp.) *Bicyclic pyranone derivatives as nicotinic acid receptor agonists*. WO 2010075069.

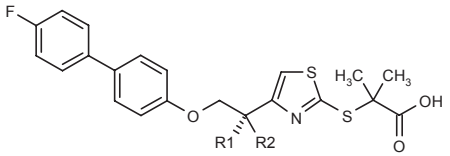
704114

2-[4-[2-(4'-Fluorobiphenyl-4-yloxy)-1-hydroxyethyl]thiazol-2-ylsulfanyl]-2-methylpropionic acid



C21H20FNO4S2; Mol wt: 433.5160

ACTION – Peroxisome proliferator-activated receptor PPARα agonist (EC_{50} = 8.4 nmol/L in luciferase assays). When administered to rats at 0.3 mg/kg p.o. for 4 days it decreased blood triglyceride levels by 56%. A 5-day treatment at the same dose in rats fed a cholesterol-rich diet led to a decrease in blood triglyceride and total blood cholesterol levels of 38 and 34%, respectively. Expected to be useful for the treatment of hyperlipidemia. Other representative compounds are:



Compound	R1	R2	Formula
704116	-O-		$C_{21}H_{18}FNO_4S_2$
704119	OH	H	$C_{21}H_{20}FNO_4S_2$

SOURCE – Mitsubishi Tanabe Pharma.

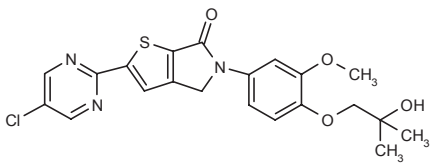
REFERENCES

1. Ando, N. (Mitsubishi Tanabe Pharma Corp.) *Carboxylic acid derivative containing thiazole ring and pharmaceutical use thereof*. WO 2010064633.

TREATMENT OF OBESITY AND NUTRITIONAL DISORDERS

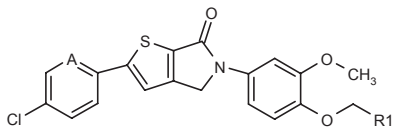
694230

2-(5-Chloropyrimidin-2-yl)-5-[4-(2-hydroxy-2-methylpropoxy)-3-methoxyphenyl]-5,6-dihydro-4*H*-thieno[2,3-*c*]pyrrol-6-one



C21H20ClN3O4S; Mol wt: 445.9190

ACTION – Melanin-concentrating hormone MCH1 receptor antagonist (K_i = 17 nM in binding assays). When administered at 30 mg/kg p.o. to rats compound reduced body weight by 4.8%. Described as useful for the treatment of obesity and diabetes, as well as anxiety, depression and inflammatory bowel disease. Related compounds include:



Compound	R1	A	Formula
694227	(S)-CH(OH)CH2SO2Me	N	$C_{22}H_{21}ClN_2O_6S_2$
694229	C(Me)2OH	CH	$C_{23}H_{22}ClNO_4S$

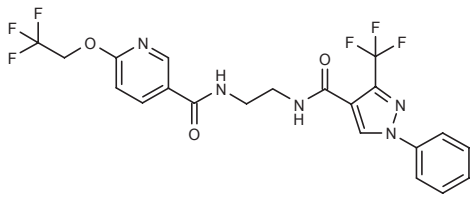
SOURCE – Bristol-Myers Squibb.

REFERENCES

1. Zhao, G. et al. (Bristol-Myers Squibb Co.) *Pyrrolone melanin concentrating hormone receptor-1 antagonists*. WO 2010042674.

695647

N-[2-[1-Phenyl-3-(trifluoromethyl)-1*H*-pyrazol-4-ylcarboxamido]-ethyl]-6-(2,2,2-trifluoroethoxy)pyridine-3-carboxamide



C21H17F6N5O3; Mol wt: 501.3818

ACTION – Diacylglycerol *O*-acyltransferase 1 Inhibitor that displayed IC_{50} values of 22 and 44 nM, respectively, in enzyme and cell-based assays. Compound 3 mg/kg b.i.d. p.o. for 4 weeks significantly reduced body weight gain (75%) and white adipose tissue weight (mesenteric 25%, perirenal 12% and subcutaneous 2.8%) without affecting total food intake in C57BL/6 mice. It showed good oral bioavailability in rats (50%). Claimed for use in the treatment of obesity, diabetes and hyperlipidemia.

SOURCES – Array BioPharma; Takeda.

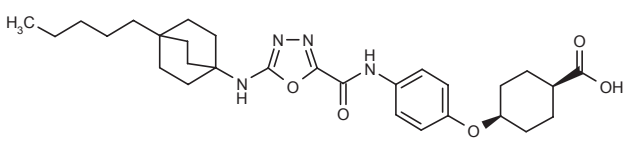
REFERENCES

1. Kitamura, S. et al. (Takeda Pharmaceutical Co., Ltd.) *Amide compounds*. EP 2044055, JP 2009544616, WO 2008011131.

2. Nakada, Y. et al. *Novel acyl coenzyme A (CoA): Diacylglycerol acyltransferase-1 inhibitors: Synthesis and biological activities of diacylethylenediamine derivatives*. Bioorg Med Chem 2010, 18(7): 2785.

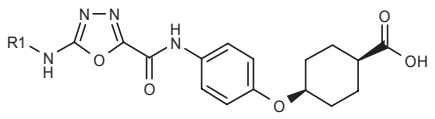
702303

cis-4-[4-[5-(4-Pentylbicyclo[2.2.2]oct-1-ylamino)-1,3,4-oxadiazol-2-ylcarboxamido]phenoxy]cyclohexanecarboxylic acid



C29H40N4O5; Mol wt: 524.6517

ACTION – Diacylglycerol *O*-acyltransferase 1 inhibitor (IC_{50} = 3 nM in membranes isolated from Sf9 cells), reported to be useful for the treatment of obesity, as well as type 2 diabetes and fatty liver diseases. Related compounds include:



Compound	R1	Formula
702310	(S)-CH(Me)Ph	$C_{24}H_{26}N_4O_5$
702311	3-F-PhCH2	$C_{23}H_{23}FN_4O_5$
702312	4-F-PhCH2CH2	$C_{24}H_{25}FN_4O_5$
702313	cyclohexyl-CH2CH2	$C_{24}H_{32}N_4O_5$

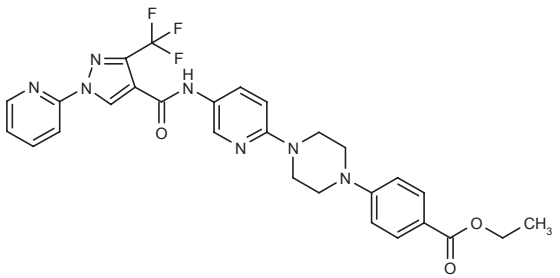
SOURCE – Astellas Pharma.

REFERENCES

1. Kawano, T. et al. (Astellas Pharma Inc.) *Oxadiazole compound*. JP 2010132590.

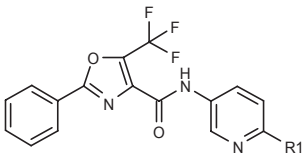
702503

4-[4-[5-[1-(2-Pyridyl)-3-(trifluoromethyl)-1*H*-pyrazol-4-ylcarboxamido]pyridin-2-yl]piperazin-1-yl]benzoic acid ethyl ester

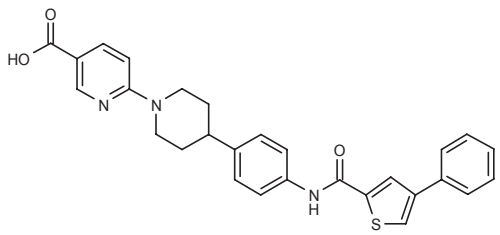


C28H26F3N7O3; Mol wt: 565.5463

ACTION – Diacylglycerol *O*-acyltransferase inhibitor (IC_{50} = 0.036 μM), potentially useful for the treatment of obesity, type 2 diabetes, dyslipidemia and metabolic syndrome. Related compounds include:



Compound	R1	Formula
702504	4-Ph-1-Piz	$C_{26}H_{22}F_3N_5O_2$
702506	4-(4-CO2H-Ph)-1-Piz	$C_{27}H_{22}F_3N_5O_4$
702508	4-(3-i-Pr-1,2,4-oxadiazol-5-yl)-1-Pip	$C_{26}H_{25}F_3N_6O_3$
702509	4-(3-Me-1,2,4-oxadiazol-5-yl)-1-Pip	$C_{24}H_{21}F_3N_6O_3$
702510	4-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1-Pip	$C_{26}H_{23}F_3N_6O_3$



702511: C28H25N3O3S

SOURCE – VIA Pharmaceuticals.

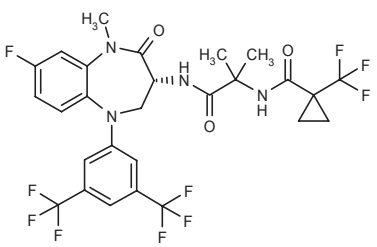
REFERENCES

1. Bolin, D.R. et al. (VIA Pharmaceuticals, Inc.) *Inhibitors of diacylglycerol acyltransferase*. US 2010152445, WO 2010077861.

704725

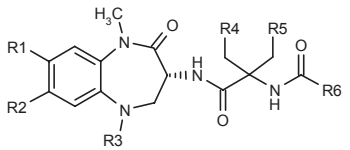
N-[5-[3,5-Bis(trifluoromethyl)phenyl]-8-fluoro-1-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3(*R*)-yl]-2-methyl-*N*^{2}-[1-(trifluoromethyl)cyclopropylcarbonyl]alaninamide

N-[1-[*N*-[5-[3,5-Bis(trifluoromethyl)phenyl]-8-fluoro-1-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3(*R*)-yl]carbamoyl]-1-methylethyl]-1-(trifluoromethyl)cyclopropanecarboxamide



C27H24F10N4O3; Mol wt: 642.4885

ACTION – Diacylglycerol *O*-acyltransferase 1 inhibitor (IC_{50} = 16.3 nM), reported to be useful for the treatment of obesity, diabetes and hyperlipidemia. Related compounds include:



Compound	R1	R2	R3	R4	R5	R6	Formula
704704	F	H	4-(CF3O)-Ph	H	H	1-Pip	$C_{27}H_{31}F_4N_5O_4$
704707	F	H	3,5-(Cl)2-Ph	H	H	t-BuNH	$C_{25}H_{30}Cl_2FN_5O_3$
704710	F	H	3,5-(CF3)2-PhCH2	bond		Ph	$C_{30}H_{25}F_7N_4O_3$
704712	H	F	3,5-(Cl)2-Ph	H	H	4-F-Ph	$C_{27}H_{24}Cl_2F_2N_4O_3$
704719	H	H	4-(CF3O)-PhCH2	bond		t-BuO	$C_{27}H_{31}F_3N_4O_5$
704722	F	H	3,5-(Cl)2-Ph	H	H	2-thiazolyl	$C_{24}H_{22}Cl_2FN_5O_3S$
704724	F	H	3,5-(CF3)2-Ph	H	H	5-F-2-Pyr	$C_{28}H_{23}F_8N_5O_3$

SOURCE – Banyu.

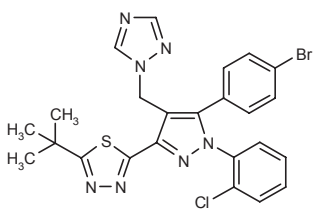
REFERENCES

1. Asai, M. et al. (Banyu Pharmaceutical Co., Ltd.) *Benzodiazepin-2-on derivatives*. WO 2010084979.

GCC-2680

705865

2-[5-(4-Bromophenyl)-1-(2-chlorophenyl)-4-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-pyrazol-3-yl]-5-*tert*-butyl-1,3,4-thiadiazole



C24H21BrClN7S; Mol wt: 554.8920

ACTION – Selective cannabinoid CB1 receptor antagonist (IC_{50} = 0.681 and 549 nM, respectively, for rat CB1 and human CB2 receptors), with selectivity over cytochrome P450 enzymes (IC_{50} > 20 μM) and the hERG channel (IC_{50} = 10.5 μM). Oral bioavailability was 67.6% in rats. No toxicity was observed in rats after treatment with up to 2000 mg/kg p.o. and compound 10 mg/kg p.o. suppressed overnight food intake in *ob/ob*, *db/db* and DIO mice, with a significant decrease in body weight gain. Potentially useful for the treatment of obesity, attention deficit disorder, Parkinson's disease, dementia, chronic intestinal pseudo-obstruction, liver cirrhosis and asthma.

SOURCE – Green Cross.

REFERENCES

1. Lee, J. et al. (Green Cross Corp.) *Heteroaryl-pyrazole derivatives as cannabinoid CB1 receptor antagonists*. EP 2097410, JP 2010504961, US 2008081815, WO 2008039023.

2. Lee, J. et al. (Green Cross Corp.) *Heteroaryl-pyrazole derivatives as cannabinoid CB1 receptor antagonists*. US 2008081812.

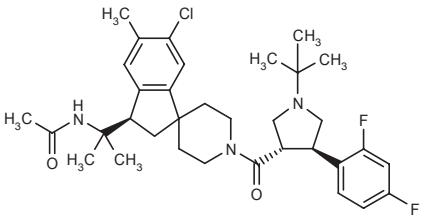
3. Lee, J. *Discovery of GCC2680 as a potent, selective and orally efficacious cannabinoid-1 receptor antagonist*. 1st Annu Int Conf Medichem (May 18-20, Beijing) 2010, Abst.

4. Lee, J. et al. *Discovery of 2-(4-((1H-1,2,4-triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-1H-pyrazol-3-yl)-5-tert-butyl-1,3,4-thiadiazole (GCC2680) as a potent, selective and orally efficacious cannabinoid-1 receptor antagonist*. Bioorg Med Chem 2010, 18(17): 6377.

MK-0489[1-4]

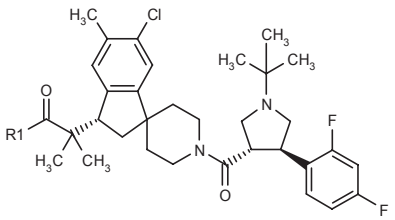
694833

N-[2-[1'-[1-*tert*-Butyl-4(*R*)-(2,4-difluorophenyl)pyrrolidin-3(*S*)-ylcarbonyl]-6-chloro-5-methyl-2,3-dihydrospiro[indene-1,4'-piperidin]-3(*R*)-yl]propan-2-yl]acetamide



C34H44ClF2N3O2; Mol wt: 600.1820

ACTION – Selective melanocortin MC4 receptor agonist (IC_{50} = 13, 1938 and 890 nM, respectively, for human MC4, MC1 and MC3 receptors in a binding assay; EC_{50} = 4.9, 1020 and 351 nM, respectively, in cAMP assays). Oral bioavailability was 33, 71 and 53%, respectively, in rats, dogs and monkeys. Doses of 10 and 6 mg/kg p.o., respectively, reduced food intake and body weight in diet-induced obese rats and mice, but not in MC4/MC3 receptor-knockout mice. Compound induced penile erection in conscious rats (maximum effective dose = 0.1 mg/kg i.v.). Reported to be useful for the treatment of obesity and erectile dysfunction. Other related compounds are:



Compound	R1	Formula
702265[2,4]	N(Me)2	$C_{35}H_{46}ClF_2N_3O_2$
702266[2,4]	3,3-(F)2-1-azetidinyl	$C_{36}H_{44}ClF_4N_3O_2$

SOURCE – Merck & Co.

REFERENCES

1. Chen, A.M. et al. (Merck & Co., Inc.) *Synthesis and crystalline forms of melanocortin-4 receptor agonist*. US 2009131465.

2. Guo, L. et al. (Merck & Co., Inc.) *Acylated spiropiperidine derivatives as melanocortin-4 receptor agonists*. CA 2520114, EP 1613601, JP 2006522132, US 2006183904, US 7329673, WO 2004089307.

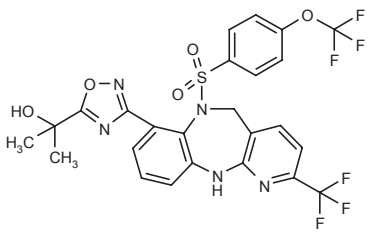
3. He, S. et al. *Discovery of a spiroindane based compound as a potent, selective, orally bioavailable melanocortin subtype-4 receptor agonist*. Bioorg Med Chem Lett 2010, 20(7): 2106.

4. He, S. et al. *Spiroindane based amides as potent and selective MC4R agonists for the treatment of obesity*. Bioorg Med Chem Lett 2010, 20(15): 4399.

MK-7725*

631255

2-[3-[6-[4-(Trifluoromethoxy)phenylsulfonyl]-2-(trifluoromethyl)-6,11-dihydro-5*H*-pyrido[2,3-*b*][1,5]benzodiazepin-7-yl]-1,2,4-oxadiazol-5-yl]propan-2-ol



C25H19F6N5O5S; Mol wt: 615.5040

ACTION – Bombesin BB3 receptor agonist (IC_{50} = 3.7 nM, EC_{50} = 11 nM for the human receptor) that reduced food intake in female obese dogs at 15 mg/kg p.o. Oral bioavailability was 93 and 100%, respectively, in rats and dogs. Potentially useful for the treatment of obesity and diabetes.

SOURCE – Merck & Co.

REFERENCES

1. Baker, R.K. et al. (Merck & Co., Inc.) *Substituted diazepine sulfonamides as bombesin receptor subtype-3 modulators*. EP 2102201, JP 2010512387, WO 2008073311.

2. Chobanian, H. et al. *Discovery of MK-7725, a potent and selective BRS-3 agonist for the treatment of obesity*. 32nd Natl Med Chem Symp (June 6-9, Minneapolis-St. Paul) 2010, Abst 5.

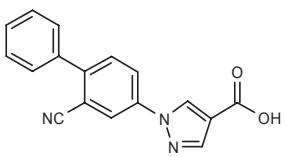
*Identified compound **631255** (see **631237**) Drug Data Rep 2008, 030(06): 0561.

TREATMENT OF DISORDERS OF PURINE AND PYRIMIDINE METABOLISM

AS-1924601-00*

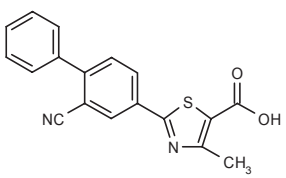
450746

1-(2-Cyanobiphenyl-4-yl)-1*H*-pyrazole-4-carboxylic acid



C17H11N3O2; Mol wt: 289.2881

ACTION – Xanthine oxidase inhibitor (IC_{50} = 1.9 nM for bovine enzyme) that inhibited oxonate-induced hyperuricemia in rats (ED_{50} = 0.35 and 7.8 mg/kg p.o., respectively, after 2 and 18 h). Compound exhibited oral bioavailability of 120, 111 and 104%, respectively, in rats, dogs and monkeys. Potentially useful for the treatment of gout and hyperuricemia. Another representative compound is:



AS-1919293-00 [450743]:** C18H12N2O2S

SOURCE – Astellas Pharma.

REFERENCES

1. Kawakami, M. et al. (Astellas Pharma Inc.) *Remedy or preventive for digestive ulcer*. EP 1992361, US 2009036428, WO 2007097403.

2. Kawakami, M. et al. (Astellas Pharma Inc.) *Therapeutic agent for hypertension*. WO 2008126772.

3. Sato, J. et al. (Astellas Pharma Inc.) *Triarylcarboxylic acid derivative*. EP 1932832, US 2009018104, US 7816558, WO 2007043457.

4. Miyata, J. et al. *Triarylcarboxylic acid derivatives as novel xanthine oxidase inhibitors*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 411.

*Identified compound **450746** (see **450734**) Drug Data Rep 2007, 029(05): 0475.

Identified compound **450743 (see **450734**) Drug Data Rep 2007, 029(05): 0475.

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

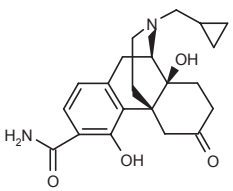
ALKS-33

469413

3-Carbamoyl-17-(cyclopropylmethyl)-4,14β-dihydroxymorphinan-6-one

17-(Cyclopropylmethyl)-4,14β-dihydroxy-6-oxomorphinan-3-carboxamide

RDC-0313



C21H26N2O4; Mol wt: 370.4421

ACTION – Opioid receptor modulator (K_i = 0.052, 0.23 and 2.6 nM, respectively, in μ, κ and δ opioid receptor binding assays) that exhibited partial agonist (EC_{50} = 1.8 and 3.3 nM, respectively, for δ and κ receptors) and antagonist activity (IC_{50} = 0.88, 6.9 and 38 nM, respectively, for μ, δ and κ receptors) in [^{35}S]-GTPγS binding assays. Compound 3 and 10 mg/kg p.o. reduced ethanol intake in rats and at 1 mg/kg s.c. and 10 mg/kg s.c/p.o. it inhibited dopamine release from nucleus accumbens in cocaine- and amphetamine-challenged rats, respectively. Oral bioavailability was 66 and 68%, respectively, in dogs and monkeys and it exhibited rapid and extensive cerebrospinal fluid penetration in monkeys. Phase I studies to evaluate safety and tolerability of single and multiple oral doses have been completed in healthy volunteers. Phase II studies to evaluate efficacy and safety in alcohol-dependent patients have been suspended and a phase II study in adults with binge eating disorder is urder way.

SOURCES – Alkermes; Rensselaer Polytechnic Institute, Troy, NY (US).

REFERENCES

1. Wentland, M.P. (Rensselaer Polytechnic Institute) *4-Hydroxybenzomorphans*. EP 1817291, JP 2008519035, US 2006111384, US 7262298, WO 2006052710.

2. Almarsson, Ö. et al. *Discovery and early development of ALKS-33, an opioid modulator for treatment of reward disorders*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 20.

3. Dean, R.L. et al. *Novel orally active opioid antagonists reduce alcohol drinking in rats*. Alcohol Clin Exp Res 2008, 32(6): 83A.

4. Li, W. and Turncliff, R. *Pharmacokinetic modeling of RDC-0313, a novel opioid receptor antagonist, in non-human primates*. Clin Pharmacol Ther 2009, 85(Suppl. 1): Abst PII-77.

5. Todtenkopf, M.S. et al. *In vitro and in vivo characterization of novel opioid antagonists*. Alcohol Clin Exp Res 2008, 32(6): 83A.

6. Turncliff, R. et al. *Predictive metabolism and bioavailability of RDC-0313, a novel opioid receptor antagonist*. Clin Pharmacol Ther 2009, 85(Suppl. 1): Abst PII-74.

7. Wentland, M.P. et al. *Discovery of carboxamide bioisosteres of the phenolic-OH of opioids*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 300.

8. Wentland, M.P. et al. *Syntheses of novel high affinity ligands for opioid receptors*. Bioorg Med Chem Lett 2009, 19(8): 2289.

9. Wentland, M.P. et al. *Synthesis and opioid receptor binding properties of a highly potent 4-hydroxy analogue of naltrexone*. Bioorg Med Chem Lett 2005, 15(8): 2107.

10. *A pilot study of RDC-0313 (ALKS 33) in adults with binge eating disorder (NCT01098435)*. ClinicalTrials.gov Web Site 2010, April 15.

11. *A study of ALKS33 (RDC-0313) in adults with alcohol Dependence (NCT00981617)*. ClinicalTrials.gov Web Site 2009, Oct 16.

12. *A study of RDC-0313 administered to healthy adults (NCT00800319)*. ClinicalTrials.gov Web Site 2008, Dec 1.

13. *Alkermes advances proprietary pipeline*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2009, April 9.

14. *Alkermes announces positive results from two clinical trials of ALKS 33*. Alkermes Press Release 2009, Oct 13.

15. *Alkermes commences new ALKS-33 trials*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2009, May 14.

16. *Alkermes initiates clinical trial for ALKS 33, a novel oral molecule with potential benefits in addiction and other CNS disorders*. Alkermes Press Release 2008, Dec 4.

17. *Alkermes initiates phase I ALKS-33 trial in healthy volunteers*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2008, Dec 5.

18. *Alkermes initiates phase II trial of ALKS-33 for alcohol dependence*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2009, Nov 19.

19. *Alkermes initiates two new clinical trials Of ALKS 33*. Alkermes Press Release 2009, May 13.

20. *Alkermes reports results from clinical trials of ALKS-33* . Thomson Reuters Drug News (formerly DailyDrugNews.com) 2009, Oct 14.

21. *Alkermes to provide update on advancing product portfolio and proprietary platforms at R&D day*. Alkermes Press Release 2010, April 26

22. *Phase 1 study to evaluate RDC-0313 coadministered with buprenorphine to opioid-experienced healthy adults (NCT01046539)*. ClinicalTrials.gov Web Site 2010, Jan 20.

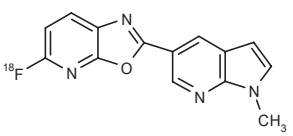
DIAGNOSTIC AGENTS

[^{18}F]-MK-3328

701922

5-[^{18}F]Fluoro-2-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxazolo[5,4-*b*]pyridine

MK-3328



C14H9FN4O; Mol wt: 267.2484

TREATMENT OF POISONING, DRUG ABUSE AND DEPENDENCY

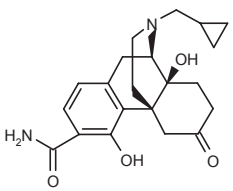
ALKS-33

469413

3-Carbamoyl-17-(cyclopropylmethyl)-4,14β-dihydroxymorphinan-6-one

17-(Cyclopropylmethyl)-4,14β-dihydroxy-6-oxomorphinan-3-carboxamide

RDC-0313



C21H26N2O4; Mol wt: 370.4421

ACTION – Opioid receptor modulator (K_i = 0.052, 0.23 and 2.6 nM, respectively, in μ, κ and δ opioid receptor binding assays) that exhibited partial agonist (EC_{50} = 1.8 and 3.3 nM, respectively, for δ and κ receptors) and antagonist activity (IC_{50} = 0.88, 6.9 and 38 nM, respectively, for μ, δ and κ receptors) in [^{35}S]-GTPγS binding assays. Compound 3 and 10 mg/kg p.o. reduced ethanol intake in rats and at 1 mg/kg s.c. and 10 mg/kg s.c/p.o. it inhibited dopamine release from nucleus accumbens in cocaine- and amphetamine-challenged rats, respectively. Oral bioavailability was 66 and 68%, respectively, in dogs and monkeys and it exhibited rapid and extensive cerebrospinal fluid penetration in monkeys. Phase I studies to evaluate safety and tolerability of single and multiple oral doses have been completed in healthy volunteers. Phase II studies to evaluate efficacy and safety in alcohol-dependent patients have been suspended and a phase II study in adults with binge eating disorder is urder way.

SOURCES – Alkermes; Rensselaer Polytechnic Institute, Troy, NY (US).

REFERENCES

1. Wentland, M.P. (Rensselaer Polytechnic Institute) *4-Hydroxybenzomorphans*. EP 1817291, JP 2008519035, US 2006111384, US 7262298, WO 2006052710.

2. Almarsson, Ö. et al. *Discovery and early development of ALKS-33, an opioid modulator for treatment of reward disorders*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 20.

3. Dean, R.L. et al. *Novel orally active opioid antagonists reduce alcohol drinking in rats*. Alcohol Clin Exp Res 2008, 32(6): 83A.

4. Li, W. and Turncliff, R. *Pharmacokinetic modeling of RDC-0313, a novel opioid receptor antagonist, in non-human primates*. Clin Pharmacol Ther 2009, 85(Suppl. 1): Abst PII-77.

5. Todtenkopf, M.S. et al. *In vitro and in vivo characterization of novel opioid antagonists*. Alcohol Clin Exp Res 2008, 32(6): 83A.

6. Turncliff, R. et al. *Predictive metabolism and bioavailability of RDC-0313, a novel opioid receptor antagonist*. Clin Pharmacol Ther 2009, 85(Suppl. 1): Abst PII-74.

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8. Wentland, M.P. et al. *Syntheses of novel high affinity ligands for opioid receptors*. Bioorg Med Chem Lett 2009, 19(8): 2289.

9. Wentland, M.P. et al. *Synthesis and opioid receptor binding properties of a highly potent 4-hydroxy analogue of naltrexone*. Bioorg Med Chem Lett 2005, 15(8): 2107.

10. *A pilot study of RDC-0313 (ALKS 33) in adults with binge eating disorder (NCT01098435)*. ClinicalTrials.gov Web Site 2010, April 15.

11. *A study of ALKS33 (RDC-0313) in adults with alcohol Dependence (NCT00981617)*. ClinicalTrials.gov Web Site 2009, Oct 16.

12. *A study of RDC-0313 administered to healthy adults (NCT00800319)*. ClinicalTrials.gov Web Site 2008, Dec 1.

13. *Alkermes advances proprietary pipeline*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2009, April 9.

14. *Alkermes announces positive results from two clinical trials of ALKS 33*. Alkermes Press Release 2009, Oct 13.

15. *Alkermes commences new ALKS-33 trials*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2009, May 14.

16. *Alkermes initiates clinical trial for ALKS 33, a novel oral molecule with potential benefits in addiction and other CNS disorders*. Alkermes Press Release 2008, Dec 4.

17. *Alkermes initiates phase I ALKS-33 trial in healthy volunteers*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2008, Dec 5.

18. *Alkermes initiates phase II trial of ALKS-33 for alcohol dependence*. Thomson Reuters Drug News (formerly DailyDrugNews.com) 2009, Nov 19.

19. *Alkermes initiates two new clinical trials Of ALKS 33*. Alkermes Press Release 2009, May 13.

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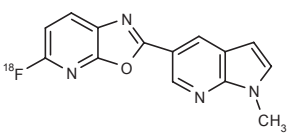
DIAGNOSTIC AGENTS

[^{18}F]-MK-3328

701922

5-[^{18}F]Fluoro-2-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxazolo[5,4-*b*]pyridine

MK-3328



C14H9FN4O; Mol wt: 267.2484

ACTION – PET tracer for imaging β-amyloid plaques (IC_{50} = 8.2 nM; K_d = 9.6 nM in binding assays) that exhibited high uptake in the thalamus and brain stem in monkeys. A phase I trial in healthy volunteers is under way to evaluate safety, radiation dosimetry, biokinetics and efficacy.

SOURCE – Merck & Co.

REFERENCES

1. Barrow, J.C. et al. (Merck & Co., Inc.) *Novel substituted azabenzoxazoles*. WO 2009155017.

2. Sur, C. and Williams, D.L. (Merck & Co., Inc.) *Novel substituted azabenzoxazoles*. WO 2010051196.

3. Harrison, S.T. et al. *Identification of the b-amyloid PET ligand candidate MK-3328*. 240th ACS Natl Meet (Aug 22-26, Boston) 2010, Abst MEDI 31.

4. Sanabria-Bohorquez, S. et al. *Development of the amylod PET radioligand [^{18}F]MK-3328*. 13th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 10-15, Honolulu) 2010, Abst P3-179.

5. Sur, C. et al. *In vitro characterization of MK-3328: A novel fluorinated positron emission tomography tracer for plaques*. 13th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 10-15, Honolulu) 2010, Abst IC-P-098.

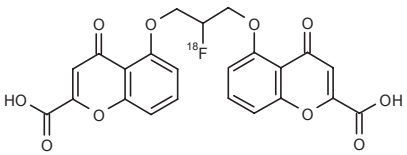
6. *Safety, radiation dosimetry, biokinetics, and effectiveness of [^{18}F]MK3328 (NCT00954538)*. ClinicalTrials.gov Web Site 2009, Dec 23.

7. *[F-18]MK-3328: Evaluation of a novel PET tracer for amyloid plaque in rhesus monkey*. NeuroImage 2010, Abst P085.

TS-734

705230

5,5'-(2-[^{18}F]Fluoropropylene-1,3-diyl)bis(oxy)bis(4-oxo-4*H*-1-benzopyran-2-carboxylic acid)



C23H15FO10; Mol wt: 469.3601

ACTION – Cromolyn derivative reported to be useful as an imaging agent and for treating atherosclerosis and Alzheimer's disease.

SOURCE – Massachusetts General Hospital, Boston, MA (US).

REFERENCES

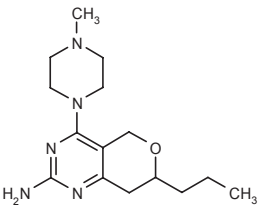
1. Elmaleh, D.R. and Shoup, T. (Massachusetts General Hospital) *Cromolyn derivatives and related methods of imaging and treatment*. WO 2010088455.

TREATMENT OF PATHOLOGICAL PROCESSES

TREATMENT OF INFLAMMATION

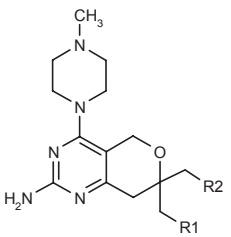
700787

4-(4-Methylpiperazin-1-yl)-7-propyl-7,8-dihydro-5*H*-pyrano[4,3-*d*]-pyrimidin-2-amine



C15H25N5O; Mol wt: 291.3919

ACTION – Histamine H4 receptor antagonist (IC_{50} = 7.9 nM at human receptors expressed in CHO cells) that inhibited histamine-induced Ca^{2+} influx in CHO cells (IC_{50} = 9 nM). Reported to be useful for the treatment of inflammatory and allergic disorders, pain, cancer and sepsis. Related compounds include:



Compound	R1	R2	Formula
700792	H	H	$C_{14}H_{23}N_5O$
700795	-(CH2)2-		$C_{16}H_{25}N_5O$

SOURCE – Dainippon Sumitomo Pharma.

REFERENCES

1. Kubota, K. et al. (Dainippon Sumitomo Pharma Co., Ltd.) *Novel 7-substituted dihydropyranopyrimidine derivative having H4 receptor antagonistic activity*. WO 2010064705.

ACTION – PET tracer for imaging β-amyloid plaques (IC_{50} = 8.2 nM; K_d = 9.6 nM in binding assays) that exhibited high uptake in the thalamus and brain stem in monkeys. A phase I trial in healthy volunteers is under way to evaluate safety, radiation dosimetry, biokinetics and efficacy.

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TS-734

705230

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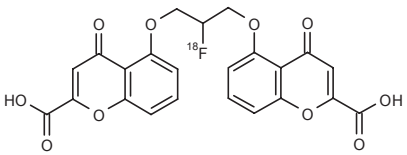

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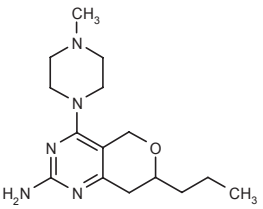
TREATMENT OF PATHOLOGICAL PROCESSES

TREATMENT OF INFLAMMATION

700787

4-(4-Methylpiperazin-1-yl)-7-propyl-7,8-dihydro-5*H*-pyrano[4,3-*d*]-pyrimidin-2-amine



C15H25N5O; Mol wt: 291.3919

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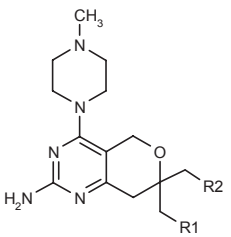


Compound	R1	R2	Formula
700792	H	H	$C_{14}H_{23}N_5O$
700795	-(CH2)2-		$C_{16}H_{25}N_5O$

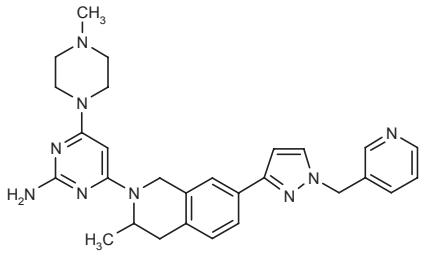
SOURCE – Dainippon Sumitomo Pharma.

REFERENCES

1. Kubota, K. et al. (Dainippon Sumitomo Pharma Co., Ltd.) *Novel 7-substituted dihydropyranopyrimidine derivative having H4 receptor antagonistic activity*. WO 2010064705.

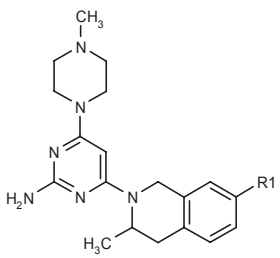
701376

4-(4-Methylpiperazin-1-yl)-6-[3-methyl-7-[1-(pyridin-3-ylmethyl)-1*H*-pyrazol-3-yl]-1,2,3,4-tetrahydroisoquinolin-2-yl]pyrimidin-2-amine isomer A



C28H33N9; Mol wt: 495.6219

ACTION – Histamine H4 receptor antagonist that reduced H4-mediated chemotaxis with an IC_{50} of 8.7 nM. Potentially useful for the treatment of inflammatory diseases including allergic rhinitis, asthma, rheumatoid arthritis, atopic dermatitis and idiopathic urticaria, pain and pruritus. Related compounds include:



Compound	R1	Formula
701371	1-(2-Pyr-CH2)-3-pyrazolyl	$C_{28}H_{33}N_9$
701374	1-(CO2Me)-4-Pip	$C_{26}H_{37}N_7O_2$
701375	1-(4-Pyr-CH2)-3-pyrazolyl	$C_{28}H_{33}N_9$

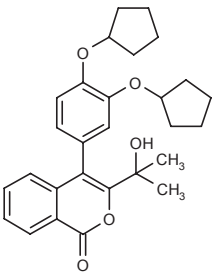
SOURCE – Incyte.

REFERENCES

1. Zhang, C. et al. (Incyte Corp.) *4,6-Disubstituted 2-amino-pyrimidines as histamine H4 receptor modulators*. US 2010173901, WO 2010075270.

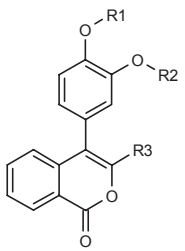
701750

4-[3,4-Bis(cyclopentyloxy)phenyl]-3-(2-hydroxypropan-2-yl)-1*H*-2-benzopyran-1-one



C28H32O5; Mol wt: 448.5507

ACTION – Phosphodiesterase inhibitor that suppressed PDE4 and PDE7 with IC_{50} values of 2.76 and 1.97 µM, respectively. Reported to be useful for the treatment of inflammation, as well as proliferative, neurological and dermatological diseases such as psoriasis, eczema, dermatitis and urticaria. Related compounds include:



Compound	R1	R2	R3	Formula
701760	cyclopentyl	CH2Ph	C(Me)2OH	$C_{30}H_{30}O_5$
701764	cyclopentyl	Bu	C(Me)2OH	$C_{27}H_{32}O_5$
701765	i-Bu	Et	C(Me)2OH	$C_{24}H_{28}O_5$
701767	Bu	Bu	C(Me)2OH	$C_{26}H_{32}O_5$
701768	Me	cyclopentyl	H	$C_{21}H_{20}O_4$

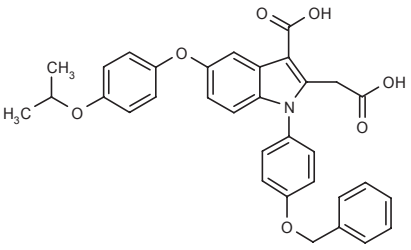
SOURCE – Biolipox.

REFERENCES

1. Pelcman, B. et al. (Biolipox AB) *Isochromenones useful in the treatment of inflammation*. WO 2010076564.

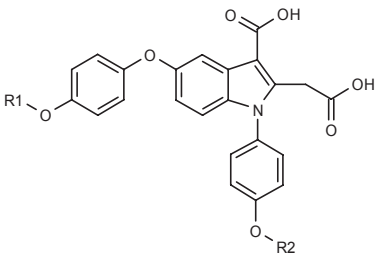
701780

1-[4-(Benzyloxy)phenyl]-2-(carboxymethyl)-5-(4-isopropoxyphenoxy)-1*H*-indole-3-carboxylic acid



C33H29NO7; Mol wt: 551.5859

ACTION – Leukotriene LTC4 synthase inhibitor that suppressed recombinant human LTC4 synthase activity expressed in *Piccia pastoralis* by 99% at 10 µM. Compound administered i.p. to mice inhibited zymosan-induced inflammation by 78, 92 and 100% at 1, 3 and 10 mg/kg, respectively. Reported to be useful for the treatment of inflammation and respiratory disorders such as asthma and chronic obstructive pulmonary diseases, as well as rhinitis, conjunctivitis, cystic fibrosis, dermatitis, urticaria, eosinophilic gastrointestinal disease, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis and pain. Related compounds include:



Compound	R1	R2	Formula
701781	i-Pr	4-Cl-Ph	$C_{32}H_{26}ClNO_7$
701783	i-Pr	2-CF3-PhCH2	$C_{34}H_{28}F_3NO_7$
701784	i-Pr	2-Pyr-CH2	$C_{32}H_{28}N_2O_7$
701786	CF3	cyclohexyl	$C_{30}H_{26}F_3NO_7$

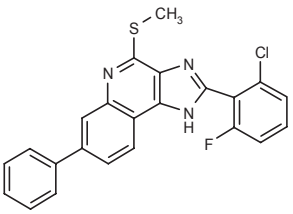
SOURCE – Biolipox.

REFERENCES

1. Nilsson, P. (Biolipox AB) *Indoles useful in the treatment of inflammation*. WO 2010076566.

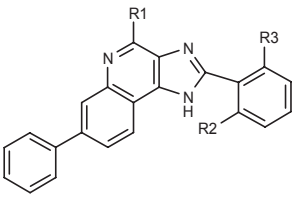
702332

2-(2-Chloro-6-fluorophenyl)-4-(methylsulfanyl)-7-phenyl-1*H*-imidazo[4,5-*c*]quinoline



C23H15ClFN3S; Mol wt: 419.9020

ACTION – Microsomal prostaglandin E synthase mPGES-1 inhibitor that reduced the activity of human mPGES-1 expressed in HEK-293 cells by 54% at 0.1 µM. Potentially useful for the treatment of inflammatory disorders such as inflammatory colitis, headache and arthritis. Related compounds include:



Compound	R1	R2	R3	Formula
702335	Cl	F	Cl	$C_{22}H_{12}Cl_2FN_3$
702337	H	CN	CN	$C_{24}H_{13}N_5$

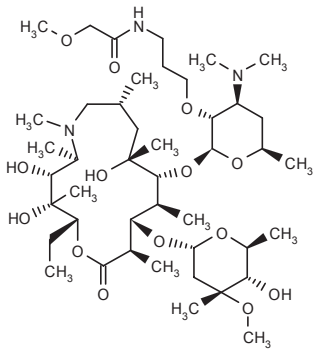
SOURCE – Dainippon Sumitomo Pharma.

REFERENCES

1. Tobe, M. and Joh, T. (Dainippon Sumitomo Pharma Co., Ltd.) *Novel imidazoquinoline derivative*. JP 2010143829.

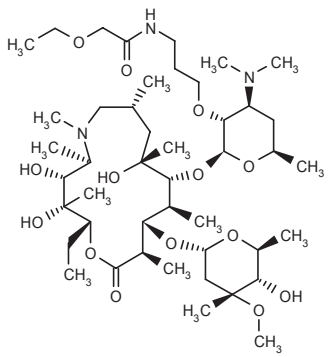
705148

9a-Aza-9-deoxo-2'-*O*-[3-(2-methoxyacetamido)propyl]-9a-methyl-9a-homoerythromycin A



C44H83N3O14; Mol wt: 878.1415

ACTION – Macrolide compound able to inhibit IL-6 production in lipopolysaccharide (LPS)-stimulated murine spleenocytes by > 40% at 50 μM. In vivo compound showed > 50% inhibition of total cell number and number of neutrophils with decrease in myeloperoxidase concentration in bronchoalveolar lavage fluid (BALF) at 100 mg/kg i.p. in BALB/cJ mice with lung neutrophilia induced by bacterial LPS. At 30 mg/kg p.o. it significantly inhibited neutrophil number by > 40% in BALF in BALB/c mice with cigarette smoke-induced lung neutrophilia. Reported to be useful for the treatment of neutrophil-dominated inflammatory diseases such as chronic obstructive pulmonary disease, cystic fibrosis, diffuse panbronchiolitis, bronchiolitis obliterans, bronchitis, bronchiectasis, acute respiratory distress syndrome, severe or steroid-resistant asthma, emphysema and chronic rhinosinusitis. Further applciations include rheumatoid arthritis, gouty arthritis, inflammatory bowel disease, atherosclerosis and psoriasis, among others. Another exemplified compound is:



705149: C45H85N3O14

SOURCE – GlaxoSmithKline.

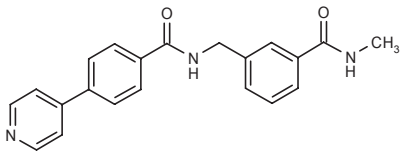
REFERENCES

1. Alihodzic, S. et al. (GlaxoSmithKline Istrazivacki Centar Zabreg DOO) *9-Deoxo-9a-methyl-9a-aza-9a-homoerythromycin a derivatives for the treatment of neutrophil dominated inflammatory diseases.* WO 2010086350.

PF-4950834

702388

N-Methyl-3-[4-(4-pyridyl)benzamidomethyl]benzamide



C21H19N3O2; Mol wt: 345.3945

ACTION – Rho-associated protein kinase ROCK-2 inhibitor (IC_{50} = 8.35 nM) with selectivity over a range of other kinases (IC_{50} = 33.12-2900 nM) that inhibited the chemokine-induced migration of human T-cell leukemia Jurkat cells (IC_{50} = 68.4 nM). Compound inhibited carrageenan-induced leukocyte infiltration in a rat air pouch model at 6 and 30 mg/kg p.o. and exhibited oral bioavailability of 100% in rats. Potentially useful for the treatment of chronic inflammatory diseases.

SOURCE – Pfizer.

REFERENCES

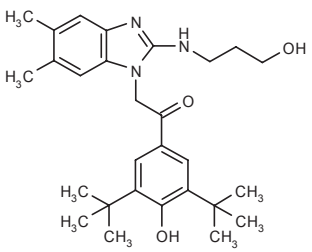
1. Rajagopalan, L.E. et al. *Biochemical, cellular, and anti-inflammatory properties of a potent, selective, orally bioavailable benzamide inhibitor of Rho kinase activity.* J Pharmacol Exp Ther 2010, 333(3): 707.

SID-17450324[1-5]

664327

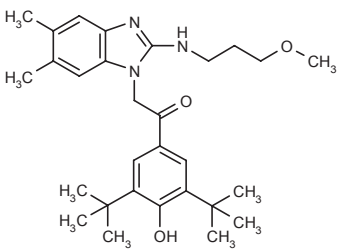
1-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2-[2-(3-hydroxypropylamino)-5,6-dimethyl-1*H*-benzimidazol-1-yl]ethanone

ChemBridge-5653914
CID-2858522



C28H39N3O3; Mol wt: 465.6276

ACTION – Nuclear factor NF-κB activation inhibitor (IC_{50} = 70 nM) that blocked phorbol myristate acetate/ionomycin-induced IL-8 production (IC_{50} = 100 nM) but did not inhibit protein kinase PKC-β and PKC-θ at up to 8 μM and was nontoxic to human hepatocytes and HEK-293 cells (LD_{50} = 47 and > 50 μM, respectively). Potentially useful for the treatment of inflammation, autoimmune diseases and cancer. Another representative compound is:



694849[1-3]**:** C29H41N3O3

SOURCES – Human Biomolecular Research Institute, San Diego, CA (US); Sanford-Burnham Medical Research Institute, La Jolla, CA (US).

REFERENCES

1. Reed, J.C. et al. (Sanford-Burnham Medical Research Institute;Human Biomolecular Research Institute) *Inhibitors of antigen receptor-induced NF-kappaB activation*. US 2009247520, WO 2009120874.

2. Okolotowicz, K.J. et al. *Selective benzimidazole inhibitors of the antigen receptor-mediated NF-κB activation pathway*. Bioorg Med Chem 2010, 18(5): 1918.

3. Peddibhotla, S. et al. *Inhibition of protein kinase C-driven nuclear factor-κB activation: Synthesis, structure-activity relationship, and pharmacological profiling of pathway specific benzimidazole probe molecules*. J Med Chem 2010, 53(12): 4793.

4. Shi, R. et al. *Chemical biology strategy reveals pathway-selective inhibitor of NF-κB activation induced by protein kinase C and antigen receptors*. Proc Am Assoc Cancer Res (AACR) 2009, 50: Abst 5364.

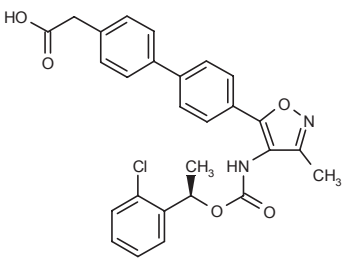
5. Shi, R. et al. *Chemical biology strategy reveals pathway-selective inhibitor of NF-κB activation induced by protein kinase C*. ACS Chem Biol 2010, 5(3): 287.

TREATMENT OF FIBROSIS

AM-966

701894

2-[4'-[4-[1(*R*)-(2-Chlorophenyl)ethoxycarbonylamino]-3-methylisoxazol-5-yl]biphenyl-4-yl]acetic acid



C27H23ClN2O5; Mol wt: 490.9350

ACTION – Orally active, selective lysophosphatidic acid receptor LPA-1 antagonist (IC_{50} = 0.017 and 0.19 μM, respectively, for inhibition of LPA-stimulated intracellular calcium release from cells expressing the human and murine receptor) with selectivity over other LPA receptors (IC_{50} = 1.7, 1.6, 7.7 and 8.6 μM, respectively, against human LPA-2, LPA-3, LPA-4 and LPA-5 receptors; IC_{50} = 25, 0.17 and 23 μM, respectively, against murine LPA-2, LPA-3 and LPA-5 receptors); it inhibited chemotaxis in human melanoma A2058 cells (IC_{50} = 138 nM), human lung fibroblast IMR-90 cells (IC_{50} = 181 nM) and mouse LPA-1 receptor-expressing CHO cells (IC_{50} = 469 nM). Compound 10 and 30 mg/kg p.o. b.i.d. for 3 days reduced vascular leakage, inflammation, lung injury and fibrosis in the mouse bleomycin-induced lung injury model. Potentially useful for the treatment of idiopathic pulmonary fibrosis and edema.

SOURCE – Amira Pharmaceuticals.

REFERENCES

1. Hutchinson, J.H. et al. (Amira Pharmaceuticals, Inc.) *Antagonists of lysophosphatidic acid receptors*. GB 2466121, US 2010152257.

2. Hutchinson, J.H. et al. (Amira Pharmaceuticals, Inc.) *Antagonists of lysophosphatidic acid receptors*. WO 2010077882.

3. Hutchinson, J.H. et al. (Amira Pharmaceuticals, Inc.) *Antagonists of lysophosphatidic acid receptors*. WO 2010077883.

4. Swaney, J.S. et al. *A novel, orally active LPA1 receptor antagonist inhibits lung fibrosis in the mouse bleomycin model*. Br J Pharmacol 2010, 160(7): 1699.